CLINICAL STUDY PROTOCOL

Title: **A Phase 1b, Randomized, Open-Label Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) in Combination With Cisplatin Plus Gemcitabine and PEGPH20 in Combination With Atezolizumab and Cisplatin Plus Gemcitabine Compared With Cisplatin Plus Gemcitabine in Subjects with Previously Untreated, Unresectable, Locally Advanced, or Metastatic Intrahepatic and Extrahepatic Cholangiocarcinoma and Gallbladder Adenocarcinoma**

Phase **1b**

Protocol Number: **HALO-110-101**

Original Protocol Date: **07 March 2017**
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Protocol Amendment 3 Date: **09 April 2019**

IND: **102770**

Sponsor: **Halozyme, Inc.**
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Placeholder for Approval Signatures

1. SYNOPSIS

Sponsor/Company

Halozyme, Inc.

Protocol Number

HALO-110-101

Study Title

A Phase 1b, Randomized, Open-Label Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) in Combination With Cisplatin Plus Gemcitabine and PEGPH20 in Combination With Atezolizumab and Cisplatin Plus Gemcitabine Compared With Cisplatin Plus Gemcitabine in Subjects With Previously Untreated, Unresectable, Locally Advanced or Metastatic Intrahepatic and Extrahepatic Cholangiocarcinoma and Gallbladder Cancers

Study Objectives

Note: The objectives described below will be evaluated in subjects with previously untreated unresectable, locally advanced, or metastatic intrahepatic and extrahepatic cholangiocarcinoma (ICC; ECC) and gallbladder adenocarcinoma.

Run-in Portion

Primary:

- To assess the safety and tolerability of (1) PEGPH20 in combination with cisplatin (CIS) and gemcitabine (GEM) (PEGCISGEM), and (2) PEGPH20 in combination with CIS, GEM, and atezolizumab (PEGCISGEMATEZO)

Secondary:

- To assess the pharmacokinetics (PK) of PEGPH20, CIS, GEM, and atezolizumab when given in combination
- To obtain an early assessment of the antitumor activity of PEGCISGEM and PEGCISGEMATEZO, as assessed by objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Exploratory:

- To characterize changes in cancer antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) from baseline
- To obtain an early assessment of the antitumor activity of PEGCISGEMATEZO, as assessed by ORR based on Immune-Modified Response Evaluation Criteria (Immune-Modified RECIST)
- To obtain an early assessment of the antitumor activity of PEGCISGEM and PEGCISGEMATEZO, as assessed by duration of response (DOR) and progression free survival (PFS) based on RECIST v1.1, and overall survival (OS)
- To assess the treatment effect of PEGCISGEM and PEGCISGEMATEZO on plasma hyaluronan (HA) levels and potential biomarkers and correlate those effects with clinical outcome

- To assess the prognostic and/or predictive value of exploratory biomarkers

Expansion Portion

Primary:

- To evaluate the efficacy of PEGCISGEMATEZO and PEGCISGEM compared with CISGEM, as assessed by ORR based on RECIST v1.1

Secondary:

- To evaluate the efficacy of PEGCISGEMATEZO and PEGCISGEM compared with CISGEM, as assessed by DOR, disease control rate (DCR; complete response [CR] + partial response [PR] + stable disease [SD]) and PFS based on RECIST v1.1 and OS
- To evaluate the efficacy of PEGCISGEMATEZO and PEGCISGEM compared with CISGEM, as assessed by ORR, DOR, PFS based on RECIST v1.1, and OS in subjects by programmed death-ligand 1 (PD-L1) expression levels
- To characterize the PK of PEGPH20, CIS, GEM, and atezolizumab when given in combination
- To characterize the PK of PEGPH20, CIS, and GEM when given in combination
- To evaluate the safety and tolerability profile of PEGCISGEM and PEGCISGEMATEZO compared with CISGEM

Exploratory:

- To evaluate the efficacy of PEGCISGEMATEZO based on Immune-Modified RECIST, as assessed by ORR and DOR
- To evaluate the efficacy of PEGCISGEMATEZO, as assessed by ORR and DOR based on Immune-Modified RECIST in subjects by PD-L1 expression levels
- To evaluate the DCR of PEGCISGEMATEZO according to Immune-Modified RECIST
- To assess the treatment effect of PEGCISGEM, PEGCISGEMATEZO and CISGEM on plasma HA levels and potential biomarkers and correlate those effects with clinical outcome
- To assess the prognostic and/or predictive value of exploratory biomarkers
- To characterize changes in CA19-9 and CEA from baseline

Study Design

This is a Phase 1b, multicenter, randomized, open-label, study of PEGCISGEM and PEGCISGEMATEZO treatments compared with CISGEM treatment in previously untreated subjects with unresectable, locally advanced or metastatic ICC, ECC, and gallbladder adenocarcinoma.

The study design includes 2 portions: an initial Run-in portion, followed by an Expansion portion.

The Run-in portion of this study will be used to evaluate the safety profile of the PEGCISGEM and PEGCISGEMATEZO treatments. The Expansion portion will evaluate the efficacy and safety of PEGCISGEM and PEGCISGEMATEZO treatments compared with CISGEM treatment.

Effective with Protocol Amendment 2, all-comers (subjects unselected for tumor HA and PD-L1 expression levels) will be enrolled in the study and subjects' tumor samples will be tested retrospectively for HA and PD-L1 expression levels.

In the Run-in portion, approximately 6 subjects will be enrolled in the PEGCISGEM arm and undergo at least 1 treatment cycle; thereafter, approximately 6 subjects will be enrolled in the PEGCISGEMATEZO arm. An additional 8 subjects may be enrolled in the Run-in portion to further assess the tolerability of PEGPH20 in either combination arm in order to establish an acceptable safety profile prior to the Expansion portion of the study.

After the Run-in portion of the study, the Expansion portion will begin. A total of approximately 65 subjects will be enrolled in the Expansion portion including approximately 50 subjects per Protocol Amendment 2 and approximately 15 additional subjects per Protocol Amendment 3.

The treatment period will consist of 21-day cycles in both the Run-in and Expansion portions of the study.

PEGPH20 will be administered at 3.0 µg/kg once weekly during Weeks 1-3 of all cycles in both portions of the study. An additional cohort of approximately 15 subjects will be enrolled in the Expansion portion under Protocol Amendment 3 who will receive PEGCISGEMATEZO, with PEGPH20 3.0 µg/kg administered twice weekly in Cycle 1 and once weekly in subsequent cycles (Table S-2), to evaluate the efficacy and safety of the PEGCISGEMATEZO combination treatment at a higher PEGPH20 dosing frequency.

The dosing schedule for atezolizumab administration in the Run-in portion will be the same as for subjects in the Expansion portion with 1200 mg atezolizumab administered 1 to 3 hours after PEGPH20 on Day 1 of each 21-day cycle for subjects receiving PEGCISGEMATEZO treatment.

For subjects receiving PEGCISGEM and PEGCISGEMATEZO treatment (Run-in and Expansion), the dosing schedule for CIS and GEM is the same during both portions, with administration of 25 mg/m^2 of CIS and 1000 mg/m^2 of GEM on Day 2 and Day 9 of each cycle.

In the CISGEM control arm (Expansion only), the dosing schedule for CIS and GEM administration will be 25 mg/m^2 of CIS and 1000 mg/m^2 of GEM on Day 1 and Day 8 of each cycle.

Treatment in both portions of the study will continue until death, withdrawal of consent from the study, disease progression, or unacceptable toxicity (further details in Section 6.1.3). Radiographic disease response/progression will be evaluated using RECIST v1.1 (see Section 8.2.15 for details on imaging/radiologic evaluation and Appendix B for details on RECIST v1.1). In addition, radiographic disease response/progression for subjects receiving PEGCISGEMATEZO treatment will also be evaluated using Immune-Modified RECIST (refer to Appendix D for further details on Immune-Modified RECIST) due to the possibility of pseudoprogression (an initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response with atezolizumab treatment). In the absence of unacceptable toxicity, subjects who meet criteria for disease progression per RECIST v1.1 while receiving atezolizumab will be permitted to continue treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the Investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Subject's written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial disease progression

Dose modifications for chemotherapy (CIS and GEM) are permitted in the Run-in and Expansion portions of the study. Dose interruptions are allowed for atezolizumab in both the Run-in and Expansion portions

of the study; however, dose modifications of atezolizumab are not allowed. PEGPH20 dose interruption and dose reductions are allowed in both portions of the study. Dose reduction of PEGPH20 to lower doses of 2.2 µg/kg and 1.6 µg/kg will be recommended if necessary based on toxicities in the Run-in portion and the Expansion portion. After dose reduction, the dose of PEGPH20 may be re-escalated to the prior dose utilized, at the Investigator's discretion, following a discussion with the Sponsor, provided there are no safety concerns. Dose modification guidelines are provided in Section 8.3 for PEGPH20, CIS and GEM. Guidance on atezolizumab dose interruption and discontinuation due to adverse events (AEs) are provided in the atezolizumab Investigator's Brochure (IB). Guidance on the allowed dose reduction levels for PEGPH20 are provided in Section 8.3.1.3 , Table 9, and Table 10. Additional dose modification guidelines for CIS and GEM are provided in the Prescribing Information of these chemotherapeutic agents.

In single-agent studies of PEGPH20 and in a Phase 1 combination study of PEGPH20 with GEM, the dose-limiting toxicities (DLTs) were musculoskeletal events (MSEs) 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 (HALO-110-101) uses an immunotherapeutic agent (atezolizumab) and dexamethasone and other steroids may suppress an immune response, steroids should only be used to treat AEs in some exceptional circumstances or at the Investigator's discretion as detailed in Section 10.12.3.

PEGPH20 and atezolizumab administration must be held if steroids are administered to treat AEs and can only be restarted once the steroid is discontinued. The only exceptions are topical, inhaled, intranasal or intra-articular steroids, thyroid-replacement hormone, and mineralocorticoids, which are allowed as described in Section 7.2 and Section 10.12.3, and low-dose steroids as described in Section 10.12.3.

In addition to study medication, all subjects in the PEGCISGEM and PEGCISGEMATEZO arms will also be administered piroxicam to reduce potential musculoskeletal symptoms often associated with PEGPH20 administration. Piroxicam (20 mg) will be administered at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. A non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator. 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, OTC drugs, and physical therapy can also be used at the Investigator's discretion.

To decrease the risk of thromboembolic (TE) events, an identified risk of PEGPH20, and based on the incidence of TE events observed in this study to date, prophylactic enoxaparin will be administered subcutaneously at 1 mg/kg/day to all subjects receiving PEGPH20 including subjects in the PEGCISGEM and PEGCISGEMATEZO arms enrolled through Protocol Amendment 2 and the additional cohort of 15 subjects enrolled under Protocol Amendment 3 receiving PEGCISGEMATEZO (details in Section 10.1.1). The dosage of enoxaparin of 1 mg/kg/day is the same as that administered in trials of PEGPH20 in combination with gemcitabine and nab-paclitaxel in pancreatic ductal adenocarcinoma (completed Study HALO-109-202 and ongoing Study HALO-109-301).

If enoxaparin is discontinued for any reason in subjects receiving PEGPH20, PEGPH20 will also be discontinued. Treatment with other drugs, however, may continue at the Investigator's discretion.

Subjects who discontinue treatment with all study drugs (PEGCISGEM/PEGCISGEMATEZO/CISGEM) will have an End of Treatment Visit and enter long-term follow-up for survival.

Subjects will be assessed for AEs and clinical laboratory evaluations as graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03.

An independent data monitoring committee (DMC) will periodically review safety data to protect subject welfare and identify potential safety signals in the Run-in and Expansion portions of the study.

In both portions of the study, tumor response will be assessed by a local reviewer after every 3 cycles based on RECIST v1.1 criteria and Immune-Modified RECIST. Scans for RECIST v1.1 and Immune-Modified RECIST may be obtained any time on or after Day 15 to allow enough time for the scan to be reviewed locally prior to the subject's next scheduled dosing visit.

A confirmatory scan is required in both portions of the study for subjects with CR or PR for confirmation of response. This confirmatory scan may be performed at the earliest 28 days after the date of the first documented response (per RECIST v1.1) (preferred) or at the next scheduled imaging timepoint, whichever is clinically indicated (details in Section 8.2.15).

A confirmatory scan is also required for subjects receiving PEGCISGEMATEZO treatment to confirm radiological disease progression, per Immune-Modified RECIST. This confirmatory scan should be obtained no sooner than 28 days after the initial scan that showed progression (this can be the next scheduled tumor assessment scan).

All scans for tumor assessments performed during the study should be archived in accordance with the standard local practice. The scans will be submitted to a central core imaging vendor selected by the Sponsor for potential central review at a later timepoint.

After the End of Treatment Visit, subjects will enter long-term follow-up during which information on the subject's survival and subsequent anticancer therapy will be obtained by the site every 12 weeks until the subject dies, is lost to follow-up, or withdraws consent. Subjects may be contacted more frequently to collect information on survival and subsequent anticancer therapy, as required, prior to important study timepoints, including DMC meetings and database locks.

Run-in Portion

In the Run-in portion, approximately 6 subjects will receive 3.0 µg/kg PEGPH20 on Day 1, Day 8, and Day 15 and 25 mg/m^2 of CIS and 1000 mg/m^2 of GEM administered on Day 2 and Day 9 of each 21-day cycle.

After the 6 subjects are treated for at least 1 cycle without significant toxicities, the PEGCISGEMATEZO arm will open and subjects in this arm will receive 3.0 µg/kg PEGPH20 on Day 1, Day 8, and Day 15 in combination with 1200 mg atezolizumab on Day 1 and 25 mg/m^2 of CIS and 1000 mg/m^2 of GEM administered on Day 2 and Day 9 of each 21-day cycle.

PEGPH20 dose reduction to a lower dose of 2.2 µg/kg or 1.6 µg/kg will be performed if necessary.

An additional 8 subjects may be enrolled in the Run-in portion to further assess the tolerability of either combination arm with PEGPH20 in order to establish an acceptable safety profile prior to the Expansion portion of the study.

The Sponsor in collaboration with the treating investigators will review all available safety data from all subjects in the Run-in portion, and the Sponsor will determine if the doses/tolerability profile is acceptable.

DLT evaluation of PEGCISGEM or PEGCISGEMATEZO treatments at a given PEGPH20 dose level will be carried out during DLT evaluation period (i.e., Cycle 1) as follows:

Initially 3 subjects will be enrolled:

- If ≤1 subjects experiences a DLT then 3 additional subjects will be enrolled.

  - If ≤1 subject experiences a DLT among the 6 enrolled subjects then the combination evaluated (PEGCISGEM or PEGCISGEMATEZO) will be considered safe.
  - If ≥2 subjects experience DLTs then PEGPH20 dose will be de-escalated to the next lower dose level (see Table S-1) and additional subjects (up to a total of 6) will be enrolled and evaluated.

- If ≥2 subjects experience a DLT, then PEGPH20 dose will be de-escalated to the next lower dose level and additional subjects (up to a total of 6) will be enrolled and evaluated.
- If the combination of PEGCISGEM is found to be safe and tolerable, the PEGCISGEMATEZO arm will be opened at the same PEGPH20 dose level found to be safe and tolerable in the PEGCISGEM arm, and the tolerability of this combination will be evaluated following the steps outlined earlier.
- The highest PEGPH20 dose level found to be safe and tolerable in PEGCISGEM arm of the Run-in portion will be utilized in the PEGCISGEM arm of the Dose Expansion portion. The highest PEGPH20 dose level found to be safe and tolerable in PEGCISGEMATEZO arm of the Run-in portion will be utilized in the PEGCISGEMATEZO arm of the Dose Expansion portion.
- Subjects who drop out during the initial 21 days of treatment without experiencing a DLT will be replaced.
- Safety evaluation will be initiated at PEGPH20 3.0 µg/kg dose level for the PEGCISGEM combination.
- Subjects who experience DLTs during Cycle 1 will be permanently discontinued from all study treatments.

Table S-1: Dose Allocation and Cohort Schedule - Run-in Portion (PEGCISGEM and PEGCISGEMATEZO treatments)

Cohort	PEGPH20 µg/kg	CIS mg/m^2	GEM mg/m^2	Atezolizumab mg
-2	1.6	25	1000	1200
-1	2.2	25	1000	1200
1	3.0	25	1000	1200

Abbreviations: CIS = cisplatin; GEM = gemcitabine; PEGPH20 = PEGylated recombinant human hyaluronidase
Note: Each treatment cycle is 21 days. Dose interruption and modifications are permitted (refer to Section 8.3 for further details).

Definition of Dose-Limiting Toxicity:

Treatment-related AEs that limit the dose of PEGPH20 or the combination (PEGCISGEM/PEGCISGEMATEZO) may be considered as DLTs. DLTs will be assessed for each subject during the 21 days following their first PEGPH20 dose and will be defined as:

- Treatment-emergent Grade ≥3 toxicity that is considered related to either PEGPH20 or the combination (PEGCISGEM/PEGCISGEMATEZO)
  - MSEs, colitis, and immune-related toxicities, infections will be considered as DLTs only if they reach Grade ≥3 severity despite adequate supportive care measures.

- Grade 3 nausea, vomiting, and diarrhea will be considered as DLTs if they persist for >72 hours despite optimal supportive care.
- Grade 4 nausea, vomiting, and diarrhea will be considered as DLTs if they reach Grade 4 severity despite optimal supportive care, irrespective of duration.

- Treatment-emergent Grade ≥3 symptomatic hepatic toxicity that is considered related to either PEGPH20 or the combination that does not resolve to Grade ≤2 within 48 hours or Grade ≥3 asymptomatic hepatic toxicity that is considered related to either PEGPH20 or the combination that does not resolve to Grade ≤1 within 3 weeks of onset with the following exception:
  - For patients with Grade 2 alkaline phosphatase abnormality at baseline, an increase to >8 × the upper limit of normal (ULN) that does not resolve to Grade ≤2 within 48 hours (if symptomatic) or that does not resolve to Grade ≤1 within 3 weeks of onset (if asymptomatic) will be considered a DLT.
- Grade 4 hepatic toxicity of any duration will be considered as a DLT.
- Grade ≥3 non-hematologic, non-hepatic organ toxicity, excluding the following:
  - Grade 3 immune-related AE that resolves to Grade ≤1 with immunosuppressant therapy within 3 weeks of its onset
  - Grade 3 autoimmune thyroiditis or other endocrine abnormality that can be managed by endocrine therapy or hormonal replacement
- Grade 3 neutropenia (asymptomatic) will not be considered a DLT; however Grade 4 neutropenia lasting 7 days or longer will be considered a DLT.
- Febrile neutropenia (defined below) will be considered as a DLT.

  Febrile Neutropenia - Fever is present, defined as an oral temperature of at least 38.0°C on at least 2 occasions within 24 hours, or a single oral temperature of at least 38.3°C, in the presence of neutropenia, defined as an absolute neutrophil count (ANC) of less than 500 cells/µl. Fever may also be defined as a rectal temperature of 38.6°C on at least 2 occasions within 24 hours, or a single rectal temperature of 39°C (FDA Guidance for Industry: Empiric Therapy of Febrile Neutropenia - Developing Antimicrobial Drugs for Treatment 1998).
- 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 the combination dosing (PEGCISGEM/PEGCISGEMATEZO) 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 in the PEGCISGEM arm must receive 1 of the 3 full planned doses of PEGPH20 and 1 complete dose each of CIS and GEM in Cycle 1.

To be considered evaluable for DLT assessment, subjects in the PEGCISGEMATEZO arm must receive 1 of the 3 full planned doses of PEGPH20 and 1 complete dose each of atezolizumab, CIS, and GEM in Cycle 1.

Subjects who experience a DLT within the first 21 days of treatment and withdraw from the study treatment 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.

Subjects who experience DLTs in the Run-in portion will be permanently discontinued from all study treatments.

Expansion Portion

Approximately 50 previously untreated subjects will be randomized in a 2:2:1 ratio into 1 of 3 treatment arms as follows:

- PEGCISGEM arm: PEGPH20 (3.0 µg/kg) + CIS (25 mg/m^2) + GEM (1000 mg/m^2)
- PEGCISGEMATEZO arm: PEGPH20 (3.0 µg/kg) + Atezolizumab (1200 mg) + CIS (25 mg/m^2) + GEM (1000 mg/m^2)
- CISGEM arm: CIS (25 mg/m^2) + GEM (1000 mg/m^2)

Randomization will be stratified by geographical region (North America and Asia) and cancer type (cholangiocarcinoma [CCA] and gallbladder).

An additional cohort of approximately 15 subjects will be enrolled in the Expansion portion under Protocol Amendment 3 and receive PEGCISGEMATEZO treatment: PEGPH20 (3.0 µg/kg) + Atezolizumab (1200 mg) + CIS (25 mg/m^2) + GEM (1000 mg/m^2).

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

Table S-2: Study Medication Dosing and Treatment Schedule

Timepoint	**PEGCISGEM Treatment**
All Cycles (21-day cycles)	
Week 1	
Day 1	PEGPH20
Day 2	CIS + GEM (24 ± 4 hours after Day 1 dose of PEGPH20)
Week 2	
Day 8	PEGPH20
Day 9	CIS + GEM (24 ± 4 hours after Day 8 dose of PEGPH20)
Week 3	
Day 15	PEGPH20
Timepoint	**PEGCISGEMATEZO Treatment**
Cycle 1 (21-day cycles)	
Week 1	
Day 1	PEGPH20 Atezolizumab (1 to 3 hours after PEGPH20)
Day 2	CIS + GEM (24 ± 4 hours after Day 1 dose of PEGPH20)
Day 4 [a]	PEGPH20

Week 2	
Day 8	PEGPH20
Day 9	CIS + GEM (24 ± 4 hours after Day 8 dose of PEGPH20)
Day 11 [a]	PEGPH20
Week 3	
Day 15	PEGPH20
Day 18 [a]	PEGPH20
Cycle 2 and Beyond	
Week 1	
Day 1	PEGPH20 Atezolizumab (1 to 3 hours after PEGPH20)
Day 2	CIS + GEM (24 ± 4 hours after Day 1 dose of PEGPH20)
Week 2	
Day 8	PEGPH20
Day 9	CIS + GEM (24 ± 4 hours after Day 8 dose of PEGPH20)
Week 3	
Day 15	PEGPH20

Timepoint	**CISGEM Treatment**
All cycles (21-day cycles)	
Week 1	
Day 1	CIS + GEM
Week 2	
Day 8	CIS + GEM

Abbreviations: CIS = cisplatin; GEM = gemcitabine; PEGPH20 = PEGylated recombinant human hyaluronidase
Note: Dose interruption and modifications are permitted (see Section 8.3 for further details).
[a] This visit is applicable to the additional cohort of ~15 subjects enrolled under Protocol Amendment 3 only.

Study Population

Males and females aged 18 years and older with previously untreated, locally advanced or metastatic ICC, ECC and gallbladder adenocarcinoma who meet the inclusion/exclusion criteria.

Inclusion Criteria

For both portions of the study, 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. Subjects must be determined to have histologically confirmed unresectable, locally advanced or metastatic adenocarcinoma of the intra- and/or extra-hepatic bile ducts and/or gallbladder. Prior to enrollment, confirmation of shipment of tissue sample to the central laboratory must be obtained. Subjects must have sufficient tissue with architectural integrity, including tumor and associated stroma, available for retrospective PD-L1 and HA testing (details will be included in a separate Laboratory Manual).

   Note: Tumor biopsies must be collected on or after the date that locally advanced or metastatic disease is documented.
3. One or more lesions measurable on computed tomography (CT) scan/ magnetic resonance imaging (MRI) scan per RECIST v1.1.
4. Subjects having ECOG Performance Status of 0 to 1.
5. Life expectancy ≥3 months.
6. Males and females aged ≥18 years.
7. Screening clinical laboratory values as follows:
   - Total bilirubin ≤1.5 × ULN, except for Gilbert's syndrome
   - Aspartate aminotransferase and alanine aminotransferase ≤2.5 × ULN (<5 × ULN is allowed if liver metastases or liver involvement are present)
   - Serum creatinine ≤1.5 mg/dL
   - Serum albumin ≥2.5 g/dL
   - Hemoglobin ≥9 g/dL (transfusion and erythropoietic agents allowed)
   - Absolute neutrophil count ≥1500 cells/mm^3
   - Platelet count ≥100,000/mm^3
8. 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).
9. For WOCBP and for men, agreement to use a highly effective contraceptive method from the time of screening throughout the study until 5 months (WOCBP) or 6 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, barrier methods, and/or true sexual abstinence.

Exclusion Criteria

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

1. Clinical evidence of deep vein thrombosis or pulmonary embolism present during the screening period.
   - Subject with superficial vein thrombosis are eligible.
   - Subjects with visceral/splanchnic vein thrombosis, that in the opinion of the Principal Investigator are primarily associated with the anatomic location of the underlying disease of metastatic biliary tract cancer, are eligible.
2. New York Heart Association Class III or IV (Appendix C) cardiac disease, atrial fibrillation, unstable angina, or myocardial infarction within the past 12 months before screening.
3. Subjects with known brain metastases.
4. History of cerebrovascular accident or transient ischemic attack.
5. History of active bleeding within the last 3 months prior to screening requiring transfusion.
6. Contraindication to heparin as per institutional guidelines.
7. Subjects must have received no previous radiotherapy, surgery, chemotherapy or investigational therapy for treatment of metastatic or locally advanced disease.
8. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), anti-programmed cell death protein 1 (anti-PD-1), and anti-Programmed death-ligand 1 (anti-PD-L1) therapeutic antibodies.
9. Prior treatment with 5-fluorouracil (FU) or GEM administered as a radiation sensitizer in the neoadjuvant and adjuvant settings surrounding surgery, during and up to 4 weeks after radiation therapy, is allowed if all toxicities have returned to baseline or ≤ Grade 1.
10. If a subject received therapy in the adjuvant setting, tumor recurrence or disease progression must have occurred no sooner than 6 months after completing the last dose of the adjuvant therapy.
11. Clinically significant pre-existing carotid artery disease.
12. Active, uncontrolled bacterial, viral, or fungal infection requiring systemic therapy.
13. Known allergy to hyaluronidase.
14. Intolerance to NSAIDs.
15. Current use of megestrol acetate or megestrol acetate-containing drugs (within 10 days of Day 1).
16. Women currently pregnant or breastfeeding.
17. Positive human immunodeficiency virus (HIV) test.
18. Active hepatitis B virus (HBV) infection, defined as having a positive hepatitis B surface antigen (HBsAg) test at screening.
    - Subjects with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study

if active HBV infection is ruled out on the basis of HBV ribonucleic acid (RNA)/deoxyribonucleic acid (DNA) viral load per local guidelines.

19. Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test at screening.
    - Subjects who have a positive HCV antibody test are eligible for the study if a polymerase chain reaction assay is negative for HCV RNA.
20. Active tuberculosis.
21. History of:
    a. Idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
    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.
22. Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, fatty liver, and inherited liver disease.
23. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells.
24. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
25. Treatment with therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to initiation of study treatment.
    - Subjects receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
26. Signs or symptoms of infection within 2 weeks prior to initiation of study treatment.
27. Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study.
    - Placement of central venous access catheter(s) (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.
28. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study.
    - Influenza vaccination should be given during influenza season only (approximately October to March in the Northern Hemisphere and approximately April through September in the Southern Hemisphere). Subjects must agree not to receive live, attenuated influenza vaccine

(e.g., FluMist®) within 28 days prior to the start of study treatment, during treatment, or within 5 months after the last dose of atezolizumab.

29. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2) within 6 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment.
30. Treatment with systemic immunosuppressive medication (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor alpha [anti-TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study.
    - Subjects who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.
    - The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for subjects with orthostatic hypotension, chronic obstructive pulmonary disease, or adrenocortical insufficiency is allowed.
    - Subjects with a history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumor assessments performed using MRI.
31. Active or history of autoimmune disease, including, but not limited to, colitis, Crohn's disease, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.*
    - Subjects with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study after discussion with and approval by the Medical Monitor.
    - Subjects with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study after discussion with and approval by the Medical Monitor.
32. Subjects with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., subjects with psoriatic arthritis) are permitted provided that they meet the following conditions:
    - Subjects with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
    - Rash must cover less than 10% of body surface area (BSA)
    - Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, fluocinolone 0.01%, desonide 0.05%, alclometasone dipropionate 0.05%)
    - No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
33. Uncontrolled tumor-related pain.

- Subjects requiring narcotic pain medication must be on a stable regimen at study entry.
- Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to start of study treatment. Subjects should be recovered from the effects of radiation. There is no required minimum recovery period.
- Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to the start of study treatment.

34. Uncontrolled hypercalcemia (>1.5 mmol/L ionized calcium or calcium >12 mg/dL or corrected serum calcium >ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy (unless bisphosphonate is used to prevent skeletal events).
35. Prior allogeneic stem cell or solid organ transplantation.
36. 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.
37. 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.
38. 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, CIS, GEM, and atezolizumab.

PEGPH20: PEGPH20 drug product is supplied as an aqueous solution containing 0.30 mg/mL PEGPH20 with 10 mM succinic acid, 130 mM NaCl and 10 mM L-methionine at pH 6.2. Each vial contains 1.0 mL (0.30 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.

Instructions for PEGPH20 preparation will be provided to sites in the pharmacy binder.

For subjects enrolled through Protocol Amendment 2, PEGPH20 (3.0 µg/kg) will be administered on Day 1, Day 8, and Day 15 of all cycles 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).

For the cohort of approximately 15 subjects enrolled under Protocol Amendment 3, PEGPH20 (3.0 µg/kg) will be administered on Day 1, Day 4, Day 8, Day 11, Day 15, and Day 18 of Cycle 1 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 Cycle 2 and beyond, PEGPH20 (3.0 µg/kg) will be administered on Day 1, Day 8 and Day 15.

Atezolizumab: Atezolizumab 1200 mg will be administered as an IV infusion over 60 minutes, 1 to 3 hours after PEGPH20 on Day 1 of each 21-day cycle. Note that in Cycle 2 and beyond, atezolizumab may be administered as an IV infusion over 30 minutes instead of 60 minutes if the first infusion in Cycle 1 is tolerated.

Cisplatin: CIS, a chemotherapeutic drug, will be administered as an IV infusion at 25 mg/m^2 over 1 hour with prior hydration and electrolyte supplementation with potassium and magnesium per individual institutional standard 24 ± 4 hours after a dose of PEGPH20 on Day 2 and Day 9 of each 21-day cycle to subjects receiving PEGCISGEM and PEGCISGEMATEZO. In the CISGEM arm, CIS will be administered on Day 1 and Day 8 of each 21-day cycle. Please refer to the current CIS package insert for the description and composition of this drug.

Gemcitabine: GEM, a chemotherapeutic drug, will be administered as an IV infusion at 1000 mg/m^2 over 30 minutes per institutional standard on Day 2 and Day 9 of each 21-day cycle after CIS in the PEGCISGEM and PEGCISGEMATEZO arms 24 ± 4 hours after a dose of PEGPH20. In the CISGEM (Control arm), GEM will be administered after CIS on Day 1 and Day 8 of each 21-day cycle. Please refer to the current GEM Prescribing Information for the description and composition of this drug.

Note: Premedication with antiemetics will be administered as standard-of-care to all subjects prior to CIS and GEM infusions. Steroids can only be administered if emesis is not controlled with other antiemetics.

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 radiologic disease progression or clinical progression or unacceptable toxicity is documented. Disease progression will be defined by the presence of the following, based on the Investigator's radiology reviewer's assessment:

- Disease progression documented by CT scan/MRI scan based on RECIST v1.1
- Disease progression for subjects treated with atezolizumab requires confirmation of progression with an additional scan obtained no sooner than 28 days after the initial scan that showed progression per Immune-Modified RECIST.

Due to the possibility of "pseudoprogression" in immunotherapy trials, subjects who meet the criteria for disease progression, per RECIST v1.1, while receiving atezolizumab will be permitted to continue treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Subject's written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial disease progression

Investigators may also discontinue study treatment if it is no longer in the best interest of the subject, following a discussion with the Sponsor.

Subjects who discontinue treatment with all study drugs will be followed every 12 weeks for survival until death, withdrawal of consent, or lost to follow-up. Subjects may be contacted more frequently to collect information on survival, as required, prior to important study timepoints, including DMC meetings and database locks.

Criteria for Evaluation

Study Endpoints

Run-in portion

Primary:

- Incidence of AEs, changes in clinical safety laboratory values, changes in cardiovascular parameters (electrocardiogram [ECG]), vital signs, and dose modifications (e.g., dose interruptions and delays)

Secondary:

- PK parameters of PEGPH20: maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), elimination rate constant (k_{el}), terminal elimination half-life ($t_{1/2}$), clearance (CL), volume of distribution (V_d), and area-under-the-concentration time curve (AUC).
- PK parameters of atezolizumab: C_{max}, C_{min}, $t_{1/2}$, AUC, V_d, and CL when applicable
- PK parameters for GEM: C_{max}, $t_{1/2}$, AUC, V_d, and CL when applicable
- PK parameters for CIS (total and unbound): C_{max}, $t_{1/2}$, AUC, V_d, and CL when applicable
- ORR based on RECIST v1.1

Exploratory:

- Change in CA19-9 from baseline
- Change in CEA from baseline
- ORR based on Immune-Modified RECIST
- DOR and PFS based on RECIST v1.1
- OS
- Changes in plasma HA from baseline
- Changes in tumor HA from baseline, when available
- Explore co-variates of safety and efficacy parameters with drug exposure as measured by plasma HA levels
- Explore co-variates of safety and efficacy parameters with exploratory biomarker responses

Expansion portion

Primary:

- ORR based on RECIST v1.1

Secondary:

- DOR, PFS, and DCR based on RECIST v1.1, and OS
- ORR, DOR, and PFS based on RECIST v1.1, and OS by PD-L1 expression levels
- PK parameters of PEGPH20: C_{max}, C_{min}, k_{el}, $t_{1/2}$, CL, V_d, and AUC

- PK parameters of atezolizumab: C_{max}, C_{min}, $t_{1/2}$, AUC, V_d, and CL when applicable
- PK parameters of GEM and CIS (bound and free): C_{max}, $t_{1/2}$, AUC, V_d, and CL when applicable
- Incidence of AEs, changes in clinical safety laboratory values, changes in cardiovascular parameters (ECG), vital signs, and dose modifications (e.g., dose interruptions and delays)

Exploratory:

- ORR and DOR based on Immune-Modified RECIST
- ORR and DOR based on Immune-Modified RECIST by PD-L1 expression levels
- DCR, as assessed by the Investigator according to Immune-Modified RECIST
- Changes in plasma HA from baseline
- Changes in tumor HA from baseline when available
- Explore co-variates of safety and efficacy parameters with drug exposure as measured by plasma HA levels
- Explore co-variates of safety and efficacy parameters with exploratory biomarker responses
- Change in CA19-9 from baseline
- Change in CEA from baseline

Safety Assessments

Safety will be assessed during the study by evaluation of AEs, dose modifications (e.g., interruptions and delays), clinical safety laboratory tests (hematology, blood chemistry, coagulation, urinalysis, viral serology, and PEGPH20 and atezolizumab immunogenicity), vital signs, 12-lead ECGs, and physical examinations.

The severity of AEs will be graded by Investigators using the NCI CTCAE Version 4.03 (at time of study initiation).

Efficacy Assessments

In the Run-in portion of the study subjects will be evaluated for efficacy endpoint ORR per RECIST v1.1.

In the Expansion portion of the study, subjects will be evaluated for efficacy endpoints ORR, DOR and PFS using RECIST v1.1 and OS. Subjects will also be evaluated for efficacy endpoint DCR using RECIST v1.1.

Pharmacokinetic Assessments

Plasma PEGPH20, GEM, CIS (bound and free), and serum atezolizumab concentrations will be measured as specified in the Study Schedule of Events.

Exploratory Assessments

In the Run-in portion, subjects may be evaluated for the efficacy endpoint ORR based on Immune-Modified RECIST. DOR and PFS may be evaluated based on RECIST v1.1. OS may also be evaluated.

In the Expansion portion efficacy endpoints ORR and DOR may be evaluated based on Immune-Modified RECIST. ORR and DOR may also be evaluated based on Immune-Modified RECIST by PD-L1 expression levels. Subjects may be evaluated for DCR per Immune-Modified RECIST criteria, as assessed by the Investigator.

In both portions of the study plasma and tumor samples will be collected from all subjects to assess tumor and blood biomarkers (such as circulating tumor DNA) as specified in the Study Schedule of Events. A whole blood sample will be collected from all subjects to correlate individual subject DNA sequence variation (e.g., exploratory single nucleotide polymorphism genotyping) with safety, tolerability, and potential clinical benefit.

If deemed clinically feasible by the Investigator, a second tumor sample may be collected at the time of disease progression per RECIST v1.1 (in all arms), loss of clinical benefit as determined by the Investigator (in the PEGCISGEM and PEGCISGEMATEZO arms only), or unacceptable toxicity (all arms). 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 chemotherapy effects and to potentially identify resistance mechanisms.

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

The treatment effect of PEGCISGEM, PEGCISGEMATEZO and CISGEM (in Expansion only) may be evaluated based on HA levels and exploratory biomarker levels in plasma and/or tumor samples.

Statistical Methods

Planned Total Sample Size

This study is planned to enroll approximately 77 to 85 subjects.

In the Run-in portion, approximately 6 subjects will receive PEGPH20 plus CIS plus GEM, then a cohort of 6 subjects will receive PEGPH20, atezolizumab, CIS, and GEM when the PEGCISGEM cohort clears the safety evaluation. Additional dosing cohorts may be evaluated in the Run-in portion if the initial dose of PEGPH20 utilized in the combinations tested is deemed unsafe and/or intolerable. An additional 8 subjects may be enrolled in the Run-in portion to further assess the tolerability of PEGPH20 in order to establish an acceptable safety profile prior to randomization in the Expansion Portion of the study.

In the Expansion portion, approximately 50 subjects will be enrolled and randomized in a 2:2:1 ratio into PEGCISGEMATEZO, PEGCISGEM, and CISGEM treatment arms, stratified by geographical region (North America and Asia) and cancer type (CCA and gallbladder).

For the approximately 50 subjects enrolled in the Expansion portion through Protocol Amendment 2, it is assumed that the addition of PEGPH20 and atezolizumab to CIS + GEM treatment increases ORR from 26% to 66%. An ORR of 26% was observed in subjects treated with CIS + GEM combination treatment in the ABC-02 trial, a Phase 3 trial enrolling 410 patients with biliary tract cancers (Valle 2010). A total of 50 subjects, 20 each in the PEGCISGEM and PEGCISGEMATEZO treatment arms and 10 in the CISGEM arm, are required to detect a treatment difference of 40% in ORR between the CISGEM and PEGCISGEMATEZO arms with a statistical power of approximately 80% at the one-sided alpha level of 0.1.

For the cohort of approximately 15 subjects enrolled in the Expansion portion under Protocol Amendment 3 receiving PEGCISGEMATEZO, assuming a more conservative ORR of 60% for the PEGCISGEMATEZO treatment is observed, the 80% confidence interval is 40%, 77%. The lower bound of 40% is higher than the ORR of 37% observed in a study of the immunotherapy agent nivolumab in combination with CIS and GEM in 30 subjects with advanced biliary tract carcinoma (Ikeda 2019).

Analysis Populations

Enrolled Population: All subjects enrolled in the Run-in portion and the Expansion portion of the study. The enrolled population will be used for the subject disposition, demographics, and baseline characteristics summaries.

Treated Population: All subjects in the Run-in and the Expansion portion of the study who receive any study medication. The Treated Population will be used for efficacy and safety analyses. Subjects will be analyzed based on the treatment received.

Efficacy Evaluable Population: Subjects in the Expansion portion who receive any study medication as randomized and have an evaluable baseline and post-baseline tumor assessment, unless discontinued from treatment because of disease progression or death. Efficacy Evaluable Population will be used as the primary analysis population for efficacy.

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

Analyses

Analysis of Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized using the Enrolled Population. The following demographic and baseline characteristics will be summarized: age, sex, race, height, weight, medical history, disease characteristics, and treatment history.

Efficacy Analyses

All efficacy analyses will be conducted using the Efficacy Evaluable population and treated population. The Efficacy Evaluable population will be the primary analysis population for efficacy. All statistical tests will be conducted at the 1-sided alpha level of 0.1. No adjustment of alpha level will be made for multiple tests.

ORR will be calculated as the number of subjects with a CR or PR divided by the number of subjects in the analysis population. For the approximately 50 subjects enrolled in the Expansion portion through Protocol Amendment 2, the treatment difference between each of the investigational arms and the control arm will be tested using the 1-sided Fisher's Exact test. Median DOR will be estimated by treatment arm using the Kaplan-Meier method. The DCR will be analyzed similarly to the ORR. For the additional cohort of approximately 15 subjects enrolled in the Expansion portion under Protocol Amendment 3 receiving PEGCISGEMATEZO, the ORR will be presented and its 80% confidence interval will be calculated using the exact method. Median DOR, DCR, and PFS in these subjects will be analyzed in a similar manner as for subjects enrolled through Protocol Amendment 2. No statistical comparison of ORR, DOR, DCR, and PFS will be made between subjects in this additional cohort and subjects enrolled prior to Protocol Amendment 3.

PFS is defined as time from randomization to radiological disease progression or death. Kaplan-Meier method will be used to estimate the median PFS and its 80% confidence interval (CI), first and third quartiles, and PFS rates at Months 6, 9, and 12 by treatment arm. The PFS comparison between the PEGCISGEM and PEGCISGEMATEZO treatment arm versus CISGEM treatment arm will be based on a 1-sided log-rank test. The hazard ratio and 80% CI for the treatment effect will be estimated using the Cox proportional hazards regression model. Estimated survival curves of PFS of the three treatment arms will be displayed graphically.

OS is defined as time from randomization to death at any time. OS will be analyzed similarly as PFS.

Safety Analyses

All safety parameters will be summarized by treatment using the Treated Population.

All AEs will be presented in incidence tables coded by the Medical Dictionary for Regulatory Activities (MedDRA) v18.0 Preferred Term and System Organ Class. Additionally, separate AE incidence tables, coded by MedDRA, will be presented by: 1) toxicity grade (severity) graded by the CTCAE and 2) relationship to study medication (PEGPH20, CIS, GEM, and atezolizumab).

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.

Pharmacokinetic Analyses

Noncompartmental analysis will be performed where possible/appropriate on PEGPH20, GEM, CIS (bound and free), and atezolizumab. The PK parameters AUC, C_{max}, C_{min}, CL, V_d, k_{el}, and $t_{1/2}$ will be summarized from noncompartmental analysis along with descriptive statistics, when applicable. Other PK analyses will be performed when appropriate.

Exploratory Analyses

Descriptive summaries will be provided for all exploratory endpoints

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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LIST OF ABBREVIATIONS

The following abbreviations are used in this protocol.

Abbreviation	Definition
^{18}F-FDG PET/CT	2-deoxy-2-[fluorine-18] fluoro- D-glucose integrated with positron emission tomography-computed tomography
ADA	anti-drug antibodies
AE	adverse event
AG	nab-paclitaxel plus gemcitabine
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-TNF-α	anti-tumor necrosis factor alpha
AST	aspartate aminotransferase
AUC	area-under-the-concentration time curve
BSA	body surface area
BUN	blood urea nitrogen
CA19-9	cancer antigen 19-9
CBC	complete blood count
CCA	cholangiocarcinoma
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	Confidence Interval
CIS	cisplatin
CISGEM	cisplatin in combination with gemcitabine
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
DCR	disease control rate

Abbreviation	Definition
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
Doc	docetaxel alone
DOR	duration of response
DVT	deep vein thrombosis
EC	Ethics Committee
ECC	extrahepatic cholangiocarcinoma
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMT	epithelial-mesenchymal transition
EOT	End of Treatment
FDA	Food and Drug Administration
FU	5-fluorouracil
GCP	Good Clinical Practice
GEM	gemcitabine
GFR	glomerular filtration rate
HA	hyaluronan
HA-high	high expression of HA
HBcAB	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator’s Brochure
ICC	intrahepatic cholangiocarcinoma
ICF	Informed Consent Form

Abbreviation	Definition
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
IUD	intrauterine device
IUS	intrauterine hormone releasing system
IV	intravenous
IWRS	Interactive Web Response System
k_{el}	elimination rate constant
KPC	$Kras^{LSL\text{-}G12D/þ}$; $Trp53^{LSL\text{-}R172H/þ}$; Cre
mAb	monoclonal antibody
MedDRA	Medical Dictionary of Regulatory Activities
MRI	magnetic resonance imaging
MSE	musculoskeletal event
MTD	maximum tolerated dose
NAB	nab-paclitaxel
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
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
PD	progressive disease
PD-1	programmed cell death-1
PDA	pancreatic ductal adenocarcinoma
PD-L1	PD-1 ligand 1
PDoc	PEGPH20 plus docetaxel
PDx	patient-derived xenografts
PE	pulmonary embolism
PEG	polyethylene glycol

Abbreviation	Definition
PEGCISGEM	PEGPH20 in combination with cisplatin and gemcitabine
PEGCISGEMATEZO	PEGPH20 in combination with cisplatin, gemcitabine, and atezolizumab
PEGPH20	PEGylated recombinant human hyaluronidase
PFS	progression-free survival
PGx	Pharmacogenetics
PH20	recombinant human hyaluronidase
PI	Principal Investigator
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
PUVA	psoralen plus ultraviolet A radiation
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
rHuPH20	recombinant human hyaluronidase
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SMQ	Standardized MedDRA Queries
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	terminal half-life
T3	triiodothyronine
T4	total thyroxine
TE	thromboembolic
TME	tumor microenvironment
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
V_d	volume of distribution
WBC	white blood cell
WOCBP	women of childbearing potential

3. STUDY SCHEDULES OF EVENTS

Table 1: Study Schedule of Events: Screening (Run-in and Expansion)

Tests and Assessments[a]	**≤28 Days Before Day 1**
Sign and date Informed Consent	X
Study procedure-associated SAE recording	X
Inclusion/exclusion criteria	X
Medical history	X
Bile duct adenocarcinoma history (intrahepatic, extrahepatic, and gallbladder adenocarcinoma)	X
Prior medication history	X
Confirm availability of 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, d]	X
Doppler ultrasound of lower extremities	X
12-Lead ECG	X
Physical examination[c]	X
Vital signs[c]	X
ECOG Performance Status	X
Height and weight/BSA[c]	X
Local Laboratory Tests	
Urine/serum pregnancy tests (WOCBP)[e]	X
Central Laboratory Tests[f]	
Hematology	X
Blood chemistry	X
Urinalysis	X

Table 1: Study Schedule of Events: Screening (Run-in and Expansion) (Continued)

Tests and Assessments[a]	≤28 Days Before Day 1
Coagulation[g]	X
Plasma HA	X
CA19-9	X
CEA	X
Plasma biomarker	X
Thyroid function tests[h]	X
Viral serologyi	X
Subject registration following signing of ICF	X
Subject enrollment (in both portions) and randomization (in Expansion only)	X

Abbreviations: BSA = body surface area; CA19-9 = cancer antigen 19-9; CEA = carcinoembryonic antigen; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; ICF = Informed Consent Form; HA = hyaluronan; INR = International normalized ratio; PT = prothrombin time; MRI = magnetic resonance imaging; PTT = partial thromboplastin time WOCBP = women of childbearing potential.

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

[b] Archived tissue from the primary or a metastatic lesion is required. Refer to the Laboratory Manual for tumor tissue requirements. Subjects' tumor samples will be tested retrospectively for HA and PD-L1 expression levels.

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

[d] Chest CT scans should be read locally to evaluate for the presence of pulmonary embolism (PE). If a subject shows signs or symptoms of PE after the initial scan was completed, the chest scan should be repeated prior to enrollment (in Run-in)/randomization (in Expansion) to assess for the presence of PE. If a PE is present, the subject will be excluded from the study.

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

[f] If central laboratory results are delayed, local laboratory results may be used to determine subject eligibility (all central laboratory testing is still required). Refer to Section 8.2.11 for further details.

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

[h] Blood samples will be collected for baseline testing of thyroid hormones (free triiodothyronine [T3 or total T3 for sites where free T3 is not performed], free total thyroxine [T4] and thyroid stimulating hormone [TSH]).

[i] Subjects will be tested for HIV (unless not permitted per local regulations) and HBsAg, HBsAb, total HBcAb, and HCV antibody. An HBV DNA test should be performed if a subject has a negative HBsAg result and a positive total HBcAb result at Screening. If a subject has a positive HCV antibody result at Screening, an HCV RNA test must also be performed to determine if the subject has an active HCV infection.

Table 2: Study Schedule of Events: PEGCISGEM and PEGCISGEMATEZO Treatments (Run-in and Expansion)

Tests and Assessments[a]	**Treatment Cycle 1 (3 weeks)**								**Treatment Cycles 2+ (Repeats every 3 weeks)**					**Confirmatory CT/MRI Scan**	**End of Cycle #3 and Every 3rd Cycle Thereafter**	**End of Treatment**[b]	**Long-Term Follow-Up**[c]
	Wk 1			**Wk 2**			**Wk 3**		**Wk 1**			**Wk 2**	**Wk 3**				
	D1	**D2**	**D4**[d]	**D8**	**D9**	**D11**[d]	**D15**	**D18**[d]	**D1**	**D2**	**D8**	**D9**	**D15**				
Confirm Eligibility Based on Inclusion/Exclusion Criteria	X																
Physical examination[e]	X								X							X	
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X			X	
ECOG Performance Status[e]	X								X							X	
Weight/BSA[e]	X								X							X	
12-lead ECG[f]																X	
Disease assessment (CT/MRI scan)[g]															X	X[h]	
Confirmatory scan for response and/or disease progression[i]														X			
Pregnancy test[j]									X								

Table 2: Study Schedule of Events: PEGCISGEM and PEGCISGEMATEZO Treatments (Run-in and Expansion) (Continued)

Tests and Assessments[a]	**Treatment Cycle 1 (3 weeks)**								**Treatment Cycles 2+ (Repeats every 3 weeks)**					**Confirmatory CT/MRI Scan**	**End of Cycle #3 and Every 3rd Cycle Thereafter**	**End of Treatment**[b]	**Long-Term Follow-Up**[c]
	Wk 1			**Wk 2**			**Wk 3**		**Wk 1**		**Wk 2**		**Wk 3**				
	D1	**D2**	**D4**[d]	**D8**	**D9**	**D11**[d]	**D15**	**D18**[d]	**D1**	**D2**	**D8**	**D9**	**D15**				
Central Laboratory Tests																	
Hematology[e]	X			X			X		X		X		X			X	
Blood chemistry (PEGCISGEM only[e])	X			X					X		X					X	
Blood chemistry (*PEGCISGEMATEZO only*[k])	*X*			*X*			*X*		*X*		*X*		*X*			*X*	
Thyroid function tests[l] *(PEGCISGEMATEZO only)*	*X*								*X*								
CA19-9[e]	X								X							X	
CEA[e]	X								X							X	
Urinalysis[e]	X								X							X	
Coagulation tests[m]																X	
PK, ADA, plasma HA, exp. biomarkers, PGx, tumor biopsy	Collection schedule and details for PK, immunogenicity (ADA), plasma HA, exploratory biomarkers, PGx, and tumor biopsy samples provided in Table 4																

Table 2: Study Schedule of Events: PEGCISGEM and PEGCISGEMATEZO Treatments (Run-in and Expansion) (Continued)

Tests and Assessments[a]	Treatment Cycle 1 (3 weeks)								Treatment Cycles 2+ (Repeats every 3 weeks)					Confirmatory CT/MRI Scan	End of Cycle #3 and Every 3rd Cycle Thereafter	End of Treatment[b]	Long-Term Follow-Up[c]
	Wk 1			Wk 2			Wk 3		Wk 1		Wk 2		Wk 3				
	D1	D2	D4[d]	D8	D9	D11[d]	D15	D18[d]	D1	D2	D8	D9	D15				
Piroxicam[n]	X		X	X		X	X	X	X		X		X				
Proton pump inhibitor[o]	X	X	X	X	X	X	X	X	X	X	X	X	X			X	
Enoxaparin administration[p]	X																
PEGPH20 administration	X		X	X		X	X	X	X		X		X				
Atezolizumab administration[q] *(PEGCISGEMATEZO only)*	*X*								*X*								
Cisplatin (CIS) administration[r]		X			X					X		X					
Gemcitabine (GEM) administration[r]		X			X					X		X					
EOT tumor biopsy[s]																X	
Concomitant medication and procedure recording	X															X	
Adverse event recording	X															X	
Long-term follow-up																	X

Abbreviations: ADA = anti-drug antibodies; BSA = body surface area; CA19-9 = cancer antigen 19-9; CEA = carcinoembryonic antigen; CT = computed tomography; D = Day; DMC = Data monitoring committee; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; exp. = exploratory; HA = hyaluronan; MRI = magnetic resonance imaging; PK = pharmacokinetics; INR = International normalized ratio; PGx = pharmacogenetics; PT = prothrombin time; PTT = partial thromboplastin time.

Note: Scheduled visits should occur within ±2 days of the specified dates as long as doses are separated by the appropriate amount of time.

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

[b] End of Treatment Visit will occur within approximately 7 days after disease progression determination or treatment discontinuation.

[c] Subjects will enter Long-Term Follow-Up after the End of Treatment Visit. The site will obtain information about the subject's survival and subsequent anticancer therapy every 12 weeks until the subject dies, is lost to follow-up, or withdraws consent. Subjects may be contacted more frequently to collect information on survival and subsequent anticancer therapy, as required, prior to important study timepoints, including DMC meetings and database locks.

[d] This visit is applicable to the cohort of ~15 subjects enrolled under Protocol Amendment 3 only.

[e] Perform the following pre-dose during all Treatment Cycles and at the End of Treatment Visit: physical examination, vital sign measurements, ECOG, weight/BSA, hematology, blood chemistry, CA19-9, CEA, and urinalysis

[f] 12-lead electrocardiogram will be done at End of Treatment and otherwise when clinically indicated.

[g] Tumor assessment scans (computed tomography [CT]/ magnetic resonance imaging [MRI] of chest, abdomen, pelvis, and other areas of known or newly suspected disease) will be obtained and read by a local reviewer at the end of Cycle 3 and at the end of every third treatment cycle thereafter (i.e., end of Week 3 of Cycles 6, 9, etc.) for response evaluation based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in subjects receiving PEGCISGEM and PEGCISGEMATEZO and Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST) in subjects receiving PEGCISGEMATEZO only. Scans may be obtained any time on or after Day 15 to allow enough time for the scan to be reviewed locally prior to the subject's next scheduled dosing visit. All scans for tumor assessments performed during the study should be archived in accordance with the standard local practice. The scans will be submitted to a central imaging vendor selected by the Sponsor for potential central review at a later timepoint. For subjects who are withdrawn from the study due to clinical disease progression, a CT scan should be requested as soon as possible after clinical progression is determined.

[h] CT should only be done if radiologic progressive disease was not documented in the previous CT scan, unless the latter was performed within the last 14 days.

[i] A confirmatory scan is required in both portions of the study for subjects with CR or PR for confirmation of response, to be performed at the earliest 28 days after the date of the first documented response (per RECIST v1.1) (preferred) or at the next scheduled imaging timepoint, whichever is clinically indicated. A confirmatory scan is required for subjects receiving PEGCISGEMATEZO treatment to confirm radiological disease progression (per Immune-Modified RECIST), to be performed no sooner than 28 days after the initial scan that showed progression (this can be the next scheduled tumor assessment scan). (Details in Section 8.2.15.)

[j] Pregnancy test will be performed at local laboratory pre-dose for women of childbearing potential (WOCBP).

[k] In subjects receiving PEGCISGEMATEZO, measurements of total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) (as part of blood chemistry) must be obtained prior to dosing (within 48 hours is acceptable) on Days 1, 8, and 15 of Cycle 1 and Day 1 of Cycle 2. Local laboratories may be used for these measurements. Dosing can only take place if AST, and ALT values are within the ranges specified in the Inclusion Criterion. For total bilirubin, dosing can take place only if the total bilirubin is ≤3.0 × ULN in Cycle 1 (Day 1, Day 8, and Day 15) and Cycle 2 Day 1. If a subject has any of the values outside the specified ranges for ALT, AST, and total bilirubin on Day 1 of Cycle 2, the Investigator should discuss further dosing plans for the subject with the Sponsor.

[l] Thyroid hormone tests (free triiodothyronine [T3], or total T3 for sites where free T3 is not performed], free total thyroxine [T4], and thyroid stimulating hormone) will be performed on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Day 1 of Cycles 3, 6, 9 etc.).

[m] Coagulation tests (PT, PTT, INR) will be performed upon determination of disease progression.

[n] Piroxicam (20 mg) will be administered at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. A non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator.

[o] 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 equivalent).

[p] During the Treatment Period, enoxaparin will be given subcutaneously at 1 mg/kg/day to subjects in the PEGCISGEM and PEGCISGEMATEZO arms enrolled through Protocol Amendment 2 and to the additional cohort of subjects enrolled under Protocol Amendment 3 receiving PEGCISGEMATEZO (see Section 10.1.1 for additional details). On PEGPH20 dosing days, enoxaparin will be administered prior to the infusion of the study medication.

[q] Atezolizumab will be given 1 to 3 hours after PEGPH20, on Day 1 of all cycles.

[r] Cisplatin (CIS) and gemcitabine (GEM) will be given 24 ± 4 hours after a dose of PEGPH20 in the PEGCISGEM and PEGCISGEMATEZO arms, on Day 2 and Day 9 in all cycles. Note: Hydration and electrolyte supplementation with potassium and magnesium must be given prior to CIS infusion per individual institutional standards. Antiemetics will be administered as standard-of-care prior to CIS and GEM infusions. Steroids can only be administered if emesis is not controlled with other antiemetics.

[s] If deemed clinically feasible by the Investigator, an End of Treatment tumor biopsy will be collected at the time of disease progression per RECIST v1.1, loss of clinical benefit as determined by the Investigator, or unacceptable toxicity.

Table 3: Study Schedule of Events: CISGEM (Control) Treatment (Expansion only)

Tests and Assessments[a]	**Treatment Cycle 1 (3 weeks)**		**Treatment Cycles 2+ (Repeats every 3 weeks)**		**Confirmatory CT/MRI Scan**	**End of Cycle #3 and Every 3rd Cycle Thereafter**	**End of Treatment**[b]	**Long-Term Follow-Up**[c]
	Week 1	**Week 2**	**Week 1**	**Week 2**				
	D1	**D8**	**D1**	**D8**				
Confirm Eligibility Based on Inclusion/Exclusion Criteria	X							
Physical examination[d]	X		X				X	
Vital signs[e]	X	X	X	X			X	
ECOG[d]	X		X				X	
Weight/BSA[d]	X		X				X	
12-Lead ECG[f]							X[f]	
Disease assessment (CT/MRI scan)[g]						X	X[h]	
Response confirmation scan[i]					X			
Pregnancy test (WOCBP), local laboratory; before dosing			X					

Table 3: Study Schedule of Events: CISGEM (Control) Treatment (Expansion only) (Continued)

Tests and Assessments[a]	Treatment Cycle 1 (3 weeks)		Treatment Cycles 2+ (Repeats every 3 weeks)		Confirmatory CT/MRI Scan	End of Cycle #3 and Every 3rd Cycle Thereafter	End of Treatment[b]	Long-Term Follow-Up[c]
	Week 1	Week 2	Week 1	Week 2				
	D1	D8	D1	D8				
Central Laboratory Tests								
Hematology[d]	X	X	X	X			X	
Blood chemistry[d]	X	X	X	X			X	
CA19-9 (serum)	X		X				X	
CEA (serum)[d]	X		X				X	
Coagulation panel (PT, PTT, INR)[j]							X	
Urinalysis[d]	X		X				X	
PK, plasma HA, exp. biomarkers, PGx, tumor biopsy		Collection schedule and details for PK, plasma HA, exploratory biomarkers, PGx and tumor biopsy samples provided in Table 5						
CIS administration[k]	X	X	X	X				
GEM administration[k]	X	X	X	X				
EOT tumor biopsy[l]							X	
Concomitant medication and procedure recording	X						X	
Adverse event recording	X						X	
Long-term follow-up[c]								X

Abbreviations: D = Day; BSA = body surface area; CA19-9 = cancer antigen 19-9; CEA = Carcinoembryonic antigen; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group [Performance Status]; EOT = End of Treatment; exp. = exploratory; HA = hyaluronan; MRI = magnetic resonance imaging; PK = pharmacokinetics; INR = international normalized ratio; PGx = pharmacogenetics; PT = prothrombin time; PTT = partial thromboplastin time;
WOCBP = women of childbearing potential

Note: Scheduled visits should occur within ±2 days of the specified dates as long as doses are separated by the appropriate amount of time.

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

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

[c] After the End of Treatment Visit, subjects will enter Long-Term Follow-up during which information on the subject's survival and subsequent anticancer therapy will be obtained by the site every 12 weeks until the subject dies, is lost to follow-up, or withdraws consent. Subjects may be contacted more frequently to collect information on survival and subsequent anticancer therapy, as required, prior to important study timepoints, including DMC meetings and database locks.

[d] The following tests and assessments will be performed pre-dose in all cycles: physical examination, ECOG, weight/BSA, hematology, blood chemistry, CA 19-9, CEA, and urinalysis

[e] Vital signs will be taken pre-dose in all cycles and at End-of-Treatment Visit.

[f] 12-lead electrocardiogram will be done at End of Treatment and otherwise when clinically indicated.

[g] Tumor assessment scans (computed tomography (CT)/ magnetic resonance imaging (MRI) of chest, abdomen, pelvis, and other areas of known or newly suspected disease) will be obtained and read by a local reviewer at the end of Cycle 3 and at the end of every third treatment cycle thereafter (i.e., end of Week 3 of Cycles 6, 9, etc.) for response evaluation based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Scans may be obtained any time on or after Day 15 to allow enough time for the scan to be reviewed locally prior to the subject's next scheduled dosing visit. All scans for tumor assessments performed during the study should be archived in accordance with the standard local practice. The scans will be submitted to a central imaging vendor selected by the Sponsor for potential central review at a later timepoint. For subjects who are withdrawn from the study due to clinical disease progression, a CT scan should be requested as soon as possible after clinical progression is determined.

[h] CT should only be done if radiologic progressive disease was not documented in the previous CT scan, unless the latter was performed within the last 14 days.

[i] A confirmatory scan is required for subjects with CR or PR for confirmation of response, to be performed at the earliest 28 days after the date of the first documented response (per RECIST v1.1) (preferred) or at the next scheduled imaging timepoint, whichever is clinically indicated (details in Section 8.2.15).

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

[k] Hydration and electrolyte supplementation with potassium and magnesium must be given prior to CIS infusion per individual institutional standards. Antiemetics will be administered as standard-of-care prior to CIS and GEM infusions. Steroids can only be administered if emesis is not controlled with other antiemetics.

[l] If deemed clinically feasible by the Investigator, an End of Treatment tumor biopsy will be collected at the time of disease progression per RECIST v1.1 or unacceptable toxicity.

Table 4: Study Schedule of Events: Pharmacokinetic, Pharmacodynamic, and Translational Medicine Sample Collection - PEGCISGEM and PEGCISGEMATEZO Treatments (Run-in and Expansion)

Visit / Cycle	Cycle Week	Cycle Day	Timepoint	Collection Window/Details	Plasma HA	Plasma Biomarkers	PEGPH20 PK (plasma)	ATEZO PK (serum) [b]	CIS PK (plasma)	GEM PK (plasma)	PEGPH20 ADA (plasma)	ATEZO ADA (serum) [b]	PGx (whole blood)	Tumor Biopsy
SCR			Screening Visit	Within -28 days prior to C1D1	X	X								X [a]
Treatment Cycle 1	Week 1	Day 1	Pre-PEGPH20 dose	Anytime prior to PEGPH20 SOI									X	
			Pre-PEGPH20 dose	Within -2 h prior to PEGPH20 SOI	X	X	X	X			X	X		
			PEGPH20 EOI	Within +2 min after PEGPH20 EOI			X							
			ATEZO EOI [b]	Within +2 min after ATEZO EOI				X						
			1 to 2 h post-ATEZO [b]	i.e., 90 min (±30 min) post-ATEZO SOI	X		X							
			5 to 7 h post-ATEZO [b]	i.e., 6 h (±1 h) post-ATEZO SOI	X		X	X						
		Day 2	24 h post-PEGPH20 dose/ (pre-CIS dose)	Within -15 min prior to CIS SOI	X	X	X	X	X					
			CIS mid-infusion	30 min post-CIS SOI (±5 min)					X					
			CIS EOI	Within +2 min after CIS EOI					X					
			Pre-GEM dose	Within -15 min prior to GEM SOI						X				
			GEM mid-infusion	15 min post-GEM SOI (±5 min)						X				
			GEM EOI	Within +2 min after GEM EOI						X				
			2 to 4 h post-GEM	i.e., 3 h (±1 h) after GEM EOI	X		X	X	X	X				

Table 4: Study Schedule of Events: Pharmacokinetic, Pharmacodynamic, and Translational Medicine Sample Collection - PEGCISGEM and PEGCISGEMATEZO Treatments (Run-in and Expansion) (Continued)

Visit / Cycle	Cycle Week	Cycle Day	Timepoint	Collection Window/Details	Plasma HA	Plasma Biomarkers	PEGPH20 PK (plasma)	ATEZO PK (serum) [b]	CIS PK (plasma)	GEM PK (plasma)	PEGPH20 ADA (plasma)	ATEZO ADA (serum) [b]	PGx (whole blood)	Tumor Biopsy
		Day 4 [d]	Pre-PEGPH20 dose	Within -2 h prior to PEGPH20 SOI	X	X	X							
			PEGPH20 EOI	Within +2 min after PEGPH20 EOI			X							
Treatment Cycle 1	Week 2	Day 8	Pre-PEGPH20 dose	Within -15 min prior to PEGPH20 SOI	X	X	X	X						
			PEGPH20 EOI	Within +2 min after PEGPH20 EOI			X							
		Day 9	Pre-CIS dose	Within -15 min prior to CIS SOI		X			X					
			CIS mid-infusion	30 min post-CIS SOI (±5 min)					X					
			CIS EOI	Within +2 min after CIS EOI					X					
			Pre-GEM dose	Within -15 min prior to GEM SOI						X				
			GEM mid-infusion	15 min post-GEM SOI (±5 min)						X				
			GEM EOI	Within +2 min after GEM EOI						X				
			2 to 4 h post-GEM	i.e., 3 h (±1 h) after GEM EOI	X		X	X	X	X				
		Day 11 [d]	Pre-PEGPH20 dose	Within -15 min prior to PEGPH20 SOI	X	X	X							
			PEGPH20 EOI	Within +2 min after PEGPH20 EOI			X							
	W3	D15	Pre-PEGPH20 dose	Within -15 min prior to PEGPH20 SOI		X	X							
			PEGPH20 EOI	Within +2 min after PEGPH20 EOI	X		X	X						

Table 4: Study Schedule of Events: Pharmacokinetic, Pharmacodynamic, and Translational Medicine Sample Collection - PEGCISGEM and PEGCISGEMATEZO Treatments (Run-in and Expansion) (Continued)

Visit / Cycle	Cycle Week	Cycle Day	Timepoint	Collection Window/Details	Plasma HA	Plasma Biomarkers	PEGPH20 PK (plasma)	ATEZO PK (serum) [b]	CIS PK (plasma)	GEM PK (plasma)	PEGPH20 ADA (plasma)	ATEZO ADA (serum) [b]	PGx (whole blood)	Tumor Biopsy
		Day 18 [d]	Pre-PEGPH20 dose	Within -15 min prior to PEGPH20 SOI	X	X	X							
			PEGPH20 EOI	Within +2 min after PEGPH20 EOI	X		X							
C2+	W1	D1	Pre-PEGPH20 dose	Within -2 h prior to PEGPH20 SOI				X			X	X		
			Pre-PEGPH20 dose	Within -15 min prior to PEGPH20 SOI		X								
EOT			End of Treatment Visit			X		X			X	X		X[c]

Abbreviations: ADA = anti-drug antibodies (i.e., immunogenicity); ATEZO = atezolizumab; C = Cycle; C2+ = Cycle 2 and beyond (repeats every 3 weeks); CIS = cisplatin; D = Day; EOI = End of Infusion; EOT = End of Treatment; GEM = gemcitabine; h = hour; HA = hyaluronan; min = minute; i.e. = *id est* (in other words); RECIST = Response Evaluation Criteria in Solid Tumors; PGx = pharmacogenetic(s); PK = pharmacokinetic(s); SCR = Screening; SOI = Start of Infusion; W = week.

[a] Tumor biopsy tissue to be obtained and assessed as per Section 8.2.20.1 at SCR (mandatory for eligibility determination).

[b] This sampling timepoint is for subjects receiving PEGCISGEMATEZO only.

[c] If deemed clinically feasible by the Investigator, an EOT tumor biopsy will be obtained at the time of disease progression (as defined per RECIST v1.1), loss of clinical benefit as determined by the Investigator, or unacceptable toxicity.

[d] This visit is applicable to the cohort of ~15 subjects enrolled under Protocol Amendment 3 only.

Table 5: Study Schedule of Events: Pharmacokinetic, Pharmacodynamic, and Translational Medicine Sample Collection - CISGEM Arm (Expansion only)

Visit / Cycle	Cycle Week	Cycle Day	Timepoint	Collection Window/Details	Plasma HA	Plasma Biomarkers	CIS PK (plasma)	GEM PK (plasma)	PGx (whole blood)	Tumor Biopsy
SCR			Screening Visit	Within -28 days prior to C1D1	X	X				X[a]
Treatment Cycle 1	Week 1	Day 1	Pre-CIS dose	Within -15 min prior to CIS SOI	X	X	X		X	
			CIS mid-infusion	30 min post-CIS SOI (±5 min)			X			
			CIS EOI	Within +2 min after CIS EOI			X			
			Pre-GEM dose	Within -15 min prior to GEM SOI				X		
			GEM mid-infusion	15 min post-GEM SOI (±5 min)				X		
			GEM EOI	Within +2 min after GEM EOI				X		
			2 to 4 h post-GEM	i.e., 3 h (±1 h) after GEM EOI			X	X		
	Week 2	Day 8	Pre-CIS dose	Within -15 min prior to CIS SOI		X	X			
			CIS mid-infusion	30 min post-CIS SOI (±5 min)			X			
			CIS EOI	Within +2 min after CIS EOI			X			
			Pre-GEM dose	Within -15 min prior to GEM SOI				X		
			GEM mid-infusion	15 min post-GEM SOI (±5 min)				X		
			GEM EOI	Within +2 min after GEM EOI				X		
C2+	W1	D1	Pre-CIS dose	Within -15 min prior to CIS SOI	X[b]	X[c]				
EOT			End of Treatment Visit			X				X[d]

(Table Abbreviations and Notes on next page)

Abbreviations: **C** = [Treatment] Cycle; **C2+** = Cycle 2 and beyond (repeats every 3 weeks); **CIS** = cisplatin; **D** = Day; **EOI** = End of Infusion; **EOT** = End of Treatment; **GEM** = gemcitabine; **h** = hour; **HA** = hyaluronan; **min** = minute; **i.e.** = id est (in other words); **RECIST** = Response Evaluation Criteria in Solid Tumors; **PGx** = pharmacogenetic(s); **PK** = pharmacokinetic(s); **SCR** = Screening; **SOI** = Start of Infusion; **W** = week.

[a] Tumor biopsy tissue to be obtained and assessed as per Section 8.2.20.1 at SCR (mandatory for eligibility determination).

[b] Sample for plasma HA to be obtained only on Cycle 2, Day 1 (does not repeat every 3 weeks).

[c] Collect sample for plasma biomarker on Day 1 of Treatment Cycles 2+ (repeats every 3 weeks).

[d] If deemed clinically feasible by the Investigator, an EOT tumor biopsy will be obtained at the time of disease progression (as defined per RECIST v1.1), loss of clinical benefit as determined by the Investigator, or unacceptable toxicity.

4. BACKGROUND AND RATIONALE

4.1. Biliary Tract Cancers

Biliary tract cancer refers to a group of cancers of the biliary tract, including gallbladder cancer and cholangiocarcinoma (CCA) of intrahepatic and extrahepatic bile ducts and cancers of the ampulla and papilla of Vater (Park 2015).

Cholangiocarcinoma

CCA is an aggressive epithelial malignancy of the bile ducts that often presents with locally advanced or metastatic disease and carries an extremely poor prognosis (Saha 2016). It is the second most common primary liver tumor after hepatocellular carcinoma and accounts for about 3% of all gastrointestinal tumors (Bergquist 2015).

Named after its presumed cell of origin, CCA tumors can arise from anywhere in the biliary tract and may be difficult to identify on the basis of histopathologic analysis alone. The disease is subclassified anatomically, with intrahepatic cholangiocarcinoma (ICC) arising from within the liver and extrahepatic cholangiocarcinoma (ECC) arising from the extra hepatic bile ducts (Saha 2016).

The epidemiology of CCA is heterogeneous, and the incidence seems to be increasing (Bergquist 2015). In the United States (US), CCA accounts for approximately 5000 deaths per year (Esnaola 2016). In Asia, high incidence rates (85/100,000) has been reported in northeast Thailand (where CCA represents approximately 85% of total primitive liver cancers) and other Asian countries, such as China and Korea (Bragazzi 2012).

Patients with CCA usually present at late stages of the disease, and symptoms might be nonspecific, such as painless jaundice, weight loss, or cholangitis. Therefore, these cancers remain difficult to diagnose and treat and their prognosis is generally poor. Approximately half of the untreated patients die within 3 to 4 months of presentation from the indirect effects of local tumor progression, bile duct obstruction, liver failure or sepsis from cholangitis and abscesses (Patel 2011).

Although 1-year mortality has improved over time, the 5-year survival is still as low as 10%. Only about one third of the patients with CCA are available for curative treatment at diagnosis (Bergquist 2015).

Surgery is the only curative treatment for CCA but few patients are candidates for potentially curative surgical resection at the time of presentation (Park 2015; Patel 2011). Moreover, the outcomes after resection with curative intent are poor. Many patients are not well enough to undergo aggressive chemotherapy or radiation therapy. Furthermore, CCAs respond poorly to these therapies. In a study published in 2010, a median survival of 11.7 months was noted when systemic therapy with cisplatin (CIS) and gemcitabine (GEM; Gemzar®) was used to treat patients with unresectable biliary tract cancers. Although treatment with this combination has being touted as the standard-of-care for all biliary tract cancers novel approaches are in need to improve the poor outcome of this rare and deadly disease (Patel 2011).

Gallbladder Cancer

Gallbladder cancer is the most common malignancy of the biliary tract, accounting for 80% to 95% of biliary tract cancers (Hundal 2014). Over 80% of the gallbladder cancer cases are adenocarcinomas and originate from the fundus (60%), body (30%), or neck (10%) of the gallbladder (Shaffer 2008).

The American Cancer Society's estimates for cancer of the gallbladder and nearby large bile ducts in the US for 2016 are as follows (American Cancer Society 2016):

- About 11,420 new cases diagnosed: 5270 in men and 6150 in women
- About 3710 deaths from these cancers: 1630 in men and 2080 in women

The incidence rates of gallbladder cancer are extraordinarily high in Latin America and Asia. Asia is a high risk continent, where an increased frequency of gallbladder cancer occurs in northern Indian females, Pakistani females, and Korean males. Ethnic rates can prevail even in different geographic locations. The Korean people have the highest incidence rate (per 100,000) of gallbladder cancer in Asia: 8.1 for males and 5.6 for females. Korean males living in Los Angeles County, California also carry the highest US ethnic incidence rate at 5.9 (Hundal 2014)

The overall mean survival rate for patients with gallbladder cancer is 6 months, with a 5-year survival rate of 5% (Hundal 2014).

Complete surgical resection is the only effective treatment for gallbladder carcinoma. As early symptoms are vague and anatomically the gallbladder lacks a serosa to limit the spreading of cancer, the diagnosis of gallbladder cancer frequently occurs at an advanced stage, typically with an abysmal prognosis (Shaffer 2008). Only 10% of patients with gallbladder carcinoma present with early-stage disease and are considered surgical candidates. Among those patients who do undergo "curative" resection, recurrence rates are high. Patients with unresectable or metastatic gallbladder cancer have a poor prognosis. The role of adjuvant therapies, including systemic chemotherapy and radiotherapy, furthermore have been reported to have only a modest therapeutic effect (Zhu 2010).

In a Phase 3 study conducted in 410 patients, including 149 patients with gallbladder cancer, the addition of CIS to GEM (CISGEM) afforded significant progression-free survival (PFS; median, 8.4 months versus 6.5 months; hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.57-0.90; p = 0.003) and overall survival (OS; median, 11.7 months versus 8.3 months; HR, 0.70; 95% CI, 0.54-0.89; p = 0.002) benefits (Zhu 2010). Although treatment with this combination may be considered as the standard-of-care for gallbladder cancer, novel approaches are in need to improve the poor outcome of this rare and deadly disease.

4.2. 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; Setälä 1999; Shepard 2015; Sironen 2011). Interaction of pericellular HA and CD44 has been shown to influence drug resistance (Toole 2008). 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), lung carcinoma (Chow 2010), and CCA (Padrnos 2016).

4.3. PEGylated Recombinant Human Hyaluronidase

Halozyme, Inc. (Halozyme) has developed an investigational new molecular entity, PEGylated recombinant human hyaluronidase (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 $Kras^{LSL\text{-}G12D/þ}$; $Trp53^{LSL\text{-}R172H/þ}$; 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 recombinant human hyaluronidase (PH20) 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 ($t_{1/2}$) and enable systemic therapeutic exposure not possible with existing recombinant human PH20 (rHuPH20), Halozyme developed a PEGylated version of rHuPH20. 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 $t_{1/2}$ of approximately 3.2 hours in rodents and 50 hours in monkeys. A population PK model of PEGPH20 combining data from 218 subjects across 4 studies (HALO-109-101, HALO-109-102, HALO-109-201, and HALO-109-202) demonstrated a $t_{1/2}$ of 14.5 hours for the initial phase and 79.2 hours for the terminal phase (Halozyme Report 18218) (as compared with <10 minutes for rHuPH20 intravenous [IV] hyaluronidase [Halozyme Clinical Study Report HALO-104-104]). The increased $t_{1/2}$ of PEGPH20 makes sustained degradation of tumor-associated HA feasible.

4.3.1. PEGPH20 and Chemotherapy

Enzymatic depletion of HA 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 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 non-small cell lung cancer (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 115.5% for PEGPH20 plus Doc (PDoc), while concomitantly increasing survival by 50% (35 days for Doc alone vs 70 days for PDoc).

4.4. 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.

In the PEGPH20 clinical development program, up to 12 February 2018, a total of 290 subjects had received PEGPH20 in clinical studies conducted by the Sponsor: in 2 completed Phase 1 studies of PEGPH20 monotherapy (HALO-109-101 and HALO-109-102), in 1 completed Phase 1b study in pancreatic cancer in combination with chemotherapy (GEM; HALO-109-201), in a completed Phase 2 study in pancreatic cancer in combination with chemotherapy (GEM plus nab-paclitaxel [NAB; Abraxane®]; HALO-109-202), in a discontinued Phase 1b study in lung cancer in combination with chemotherapy (docetaxel; HALO-107-201), in the current Phase 1b study (HALO-110-101) in subjects with cholangiocarcinoma and gallbladder adenocarcinoma, and in an ongoing Phase 1b study in lung cancer in combination with the immunotherapeutic drug pembrolizumab (HALO-107-101). Additionally randomized study medication (PEGPH20 or placebo) is being administered in combination with GEM plus NAB to HA-high subjects with Stage IV pancreatic cancer in an ongoing, double-blind Phase 3 study (HALO-109-301; number of subjects dosed with PEGPH20 unknown to the Sponsor).

4.4.1. Phase 1 Study HALO-109-101

This study enrolled 14 subjects with advanced malignancies 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.

4.4.2. 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 in subjects with advanced solid tumors, including 3 subjects with intrahepatic cholangiocarcinoma. 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 (Day 1 and Day 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. Of a total of 26 subjects enrolled in this study, 6 were treated at 3.0 µg/kg once weekly and 14 received 3.0 µg/kg twice weekly schedule. The maximum tolerated dose (MTD) was determined to be 3.0 µg/kg administered once or twice weekly.

4.4.3. Phase 1b Study HALO-109-201

This study was initiated to identify the recommended Phase 2 dose (RP2D) of PEGPH20 in combination with GEM 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 3 weeks, followed by 1 week rest. GEM was administered at 1000 mg/m^2 via IV over 30 minutes once per week for 7 weeks followed by 1 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 3 weeks in a 4-week cycle.

4.4.4. Phase 2 Study HALO-109-202

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

In April 2014, the HALO-109-202 Data Monitoring committee (DMC) reported an imbalance in thromboembolic (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 deep vein thrombosis (DVT) or pulmonary embolism (PE) as well as those subjects determined to be at high risk of TE events. Stage 1 of this study included subjects who were enrolled prior to the clinical hold (N = 146 randomized). Stage 2 included subjects enrolled after the clinical hold and subsequent protocol amendment (N = 133 randomized).

The final analysis was performed with a database lock date of 01 May 2018 (Halozyme Clinical Study Report HALO-109-202). Safety and efficacy data from this study are presented in Section 4.4.7 Safety and Section 4.4.8 Efficacy.

4.4.5. Phase 1b/2 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 PDoc 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 Doc (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 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 Doc alone (75 mg/m^2 once in each 21-day cycle).

This study was discontinued 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). TE event data from this study are provided in Section 4.4.7.2. Additional safety data are provided in the PEGPH20 Investigator's Brochure.

4.4.6. 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 arms 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 are administered as IV infusions once weekly for Weeks 1 to 3 of all treatment cycles.

4.4.7. Safety

The majority of safety data from Halozyme-sponsored clinical studies are from the largest dataset comprising the subject population of Phase 2 Study HALO-109-202 of PEGPH20 in combination with GEM and NAB compared to GEM and NAB in Stage IV PDA (N = 260 total subjects treated). Additional updated safety data are from 2 Phase 1b studies, HALO-107-201 (PEGPH20 in combination with docetaxel) in NSCLC subjects, and HALO-107-101 (PEGPH20 in combination with pembrolizumab) in NSCLC and gastric adenocarcinoma subjects.

Based on a review of the available safety data across studies up to 12 February2018, important identified risks of PEGPH20 include MSEs and TE events. Refer to the PEGPH20 Investigator's Brochure for additional safety information.

4.4.7.1. Musculoskeletal Events

Musculoskeletal adverse events (AEs) have been well documented during PEGPH20 treatment and were first observed during the monotherapy dose escalation studies. 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 (atezolizumab) and dexamethasone and other steroids may suppress an immune response, steroids should only be used when prescribed by the Investigator for management of ≥ Grade 3 MSEs that are refractory to non-steroid management (additional details in Table 9).

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).

4.4.7.2. 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 (2.5%) 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 DVT and superficial thrombophlebitis.

In completed Study HALO-109-201 of PEGPH20 in combination with GEM 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 4.4.4, an imbalance was observed in the rate of TE events between the PAG and AG (PAG) 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 PE); however, arterial events were also reported. It is 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 decreased considerably compared with that observed in Stage 1. The TE event 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 CCA and gallbladder cancers have also been reported to be elevated (Jeon 2012; Martin 2012). In a trial evaluating the efficacy of chemotherapy (single-agent GEM and CIS/GEM doublet) in advanced biliary tract cancer patients (ABC-02 trial; Valle 2010), Grade 3 or 4 DVT was reported for 2% [4/198], and Grade 3 or 4 TE events for 3.5% [7/198] of subjects treated with GEM and CIS. Grade 3 or Grade 4 PE was not reported for any patients on the study. Based on these data and on the incidence of TE events reported to date in the current study (details in Section 10.1.1), the following safety measures will be taken to safeguard subjects:

1. Subjects with clinical evidence of DVT or PE at baseline will be excluded from this trial.

2. All subjects receiving PEGPH20 will be given prophylactic enoxaparin 1 mg/kg/day for thromboprophylaxis.
3. If enoxaparin is discontinued for any reason, PEGPH20 will also be discontinued. Treatment with the other drugs, 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.

4.4.8. 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 PFS (219 days) and OS (approximately 395 days). PRs were seen in 4 of the 11 subjects who had lower HA in tissue biopsies (Halozyme Clinical Study Report HALO-109-201). 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 is developing, in collaboration with a diagnostic company, Ventana Medical Systems, Inc., a novel co-developed investigational diagnostic assay 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.

In the completed Phase 2 HALO-109-202 study, the final analysis was performed as of a database lock date of 01 May 2018. Tumor samples were collected and analyzed in a prospective-retrospective fashion using the investigational diagnostic assay. Statistical significance of efficacy endpoints was declared at the 2-sided alpha level of 0.1 per protocol.

As of 01 May 2018, of the 279 subjects comprising the ITT Population, 99.6% (278/279) of subjects in the Stage 1 + Stage 2 combined were off treatment. The median PFS was 9.2 months with PAG vs. 5.2 months with AG (HR: 0.57; p-value: 0.092) in the combined Stage 1 + Stage 2 ITT HA-high Population (n = 84 [49 PAG, 35 AG]), representing a statistically significant, 4.0-month improvement with PAG for the total HA-high study population. 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 3-month improvement in median OS, which was 11.5 months with PAG vs. 8.5 months with AG (HR: 0.92).

The clinically meaningful improvements seen with PAG, compared with AG, in both median PFS (8.6 months vs. 4.5 months; HR: 0.84; p-value: 0.748) and median OS (11.7 months vs. 7.8 months HR: 0.64; p-value: 0.281) in the Stage 2 HA-high population support 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.

4.4.9. 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 timepoints, and plasma was analyzed for PEGPH20 concentrations. PK analysis suggests that a linear 2-compartment 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. A population PK model of PEGPH20 combining data from 218 subjects across 4 studies (HALO-109-101, HALO-109-102, HALO-109-201, and HALO-109-202) demonstrated a $t_{1/2}$ of 14.5 hours for the initial phase and 79.2 hours for the terminal phase (Halozyme Report 18218). The population PK model estimates of 3.99 L for the central volume and 2.94 L for the peripheral volume are consistent with expectations for therapeutic macromolecules. The prolonged $t_{1/2}$ of PEGPH20 makes sustained depletion of tumor-associated HA feasible. Clinical experience to date (largely involving combination therapy with GEM or GEM plus NAB) 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.

4.5. Study Rationale

Cancers of the biliary tract, which include intrahepatic and extrahepatic biliary cancers and gallbladder carcinoma, are a heterogeneous group of cancers with a low incidence and high mortality. They are diagnosed at an advanced, unresectable stage. Five-year survival rates are 5% to 10% for gallbladder cancer and 10% to 40% for biliary cancers (Bang 2015). In a study published in 2010, a median survival of 11.7 months was noted when systemic therapy with CIS and GEM was used to treat patients with unresectable biliary tract cancers (Valle 2010). Although treatment with this combination is considered as the standard-of-care first line therapy for all biliary tract cancers, novel approaches are in need to improve the poor outcome of this deadly disease.

Accumulation of HA in several malignant diseases is associated with aggressive tumor type, cancer progression/metastasis, and poor prognosis (Toole 2008; Setälä 1999; Shepard 2015; Sironen 2011).

Interaction of pericellular HA and CD44 has been shown to influence drug resistance (Toole 2008). Changes in 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), lung carcinoma (Chow 2010), and CCA (Padrnos 2016).

PEGPH20 is a recombinant human hyaluronidase enzyme (rHuPH20) that has been PEGylated to increase its $t_{1/2}$ in plasma. Nonclinical data demonstrate several actions of PEGPH20 in vitro and in vivo, including catabolism of tumor-associated and stromal HA, inhibition of tumor growth, reversal of some markers of the EMT, rapid "reperfusion-like" expansion of blood vessels, decreased hypoxia, enhancement of delivery of systemic chemotherapy, and increased access of monoclonal antibodies and immune cells to the tumor. PEGPH20 is currently in Phase 3 clinical development for Stage IV previously untreated pancreatic ductal adenocarcinoma, a tumor characterized by high HA accumulation.

In clinical studies (109-201 and 109-202), PEGPH20 in combination with GEM or with NAB plus GEM has led to clinically meaningful improvements in efficacy in terms of PFS, OS, and/or objective response rate (ORR), with the greatest improvements reported in subjects whose tumors were determined to be HA-high. In a Halozyme internal research study using clinical annotated samples, 133 of the 175 ICC primary tumors were shown to be HA-high. In a Phase 1 clinical study (HALO 109-102), 3 patients with ICC were treated with PEGPH20 at 3 µg/kg; 2 of the 3 patients were shown to have a partial metabolic response when assessed by 2-deoxy-2-[fluorine-18] fluoro- D-glucose integrated with positron emission tomography-computed tomography (^{18}F-FDG PET/CT). Of the 2 patients who were shown to have a partial metabolic response, 1 had a post biopsy sample showing significant HA removal, indicating that PEGPH20 was biologically active in this patient with ICC (Padrnos 2016).

A new form of immunotherapy based on inhibition of programmed death-1 (PD-1) receptors and programmed death-ligand 1 (PD-L1) is showing promise in cancer patients and offers patients and clinicians new hope. PD-L1 is an immune-checkpoint protein expressed on tumor cells and tumor-infiltrating immune cells that downregulates antitumoral T-cell function through binding to PD-1 and B7.1 (also known as CD80) receptors (Fehrenbacher 2016). In a study conducted by Bang et.al. (Interim results of Keynote-028 study), a response rate of 17.4% (95% CI, 5.0-38.8) was observed in previously treated PD-L1 positive advanced biliary tract cancer patients when treated with monoclonal antibody (mAb) pembrolizumab (Keytruda®; a humanized antibody that targets PD-1 receptor).

This Phase 1b study will evaluate the safety and early biological activity of PEGPH20 combined with another immunotherapeutic mAb, atezolizumab (Tecentriq®) and standard-of-care chemotherapy, CIS and GEM in subjects with ICC and ECCs, and gastric adenocarcinoma. Atezolizumab an engineered, humanized, immunoglobulin 1 monoclonal anti-PD-L1 antibody blocks PD-L1-PD-1, and PD-L1-B7.1 interactions, resulting in restoration of antitumor T-cell activity and enhanced T-cell priming (Fehrenbacher 2016). The anticipated mechanism of action of PEGPH20 is to degrade HA in tumors and decompress the existing tumor vasculature, thus increasing delivery of immuno- and chemotherapeutic agents.

4.5.1. Rationale for Dose and Schedule 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 (two Phase 1 and one 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.

Additionally, in a completed Phase 2 study, HALO-109-202, in which PEGPH20 was administered twice weekly for Weeks 1 to 3 of Cycle 1, then once weekly for Weeks 1 to 3 of Cycle 2 and beyond, the dose level of 3.0 µg/kg of PEGPH20 plus NAB and GEM was shown to be tolerable.

This Phase 1b/2 study will therefore evaluate PEGPH20 at a dose of 3.0 µg/kg in combination with GEM, CIS, and atezolizumab. PEGPH20 will be administered once weekly in all cycles in both portions of the study for subjects enrolled through Protocol Amendment 2.

For the additional cohort of approximately 15 subjects to be enrolled in the Expansion portion under Protocol Amendment 3 receiving PEGCISGEMATEZO treatment, PEGPH20 3.0 µg/kg will be administered twice weekly in Cycle 1; for subsequent cycles, the PEGPH20 dosing frequency is once weekly. This additional cohort will allow the Sponsor to evaluate the efficacy and safety of the PEGCISGEMATEZO combination treatment at a higher PEGPH20 dosing frequency. The rationale for the increased PEGPH20 dosing frequency in Cycle 1, to potentially improve the therapeutic effect of treatment, is based on the following considerations:

- An exposure-response analysis of efficacy data from the completed Phase 2 study of PEGPH20 in combination with NAB and GEM in subjects with metastatic pancreatic cancer (HALO-109-202) showed improvements in PFS and OS to be associated with increased PEGPH20 exposure (Halozyme Report 18250).
- The safety profile of PEGPH20 in subjects receiving PEGCISGEMATEZO treatment to date in HALO-110-101 is not different from the overall safety profile of PEGPH20 in combination with chemotherapy or immunotherapy, including Study HALO-109-202, which represents the largest dataset to date in the PEGPH20 clinical development program (refer to Section 4.4.7 and the PEGPH20 Investigator's Brochure).
- Data from completed Phase 1 Studies HALO-109-102 and HALO-109-201 and Phase 2 Study HALO-109-202, in which PEGPH20 was administered at 3.0 µg/kg twice weekly in Cycle 1 (Section 4.4.2, Section 4.4.3, and Section 4.4.4, respectively), support the increased dosing frequency (twice weekly) in Cycle 1 for the additional cohort of subjects in the current study.
- Additionally, with the increased PEGPH20 dosing frequency in Cycle 1, the dosing schedule for the additional cohort of subjects in this study will be consistent with that in both the Phase 2 study (HALO-109-202) and Phase 3 study (HALO-109-301) of PEGPH20 in combination with NAB and GEM in pancreatic cancer.

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (TECENTRIQ® US Prescribing Information 2018). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the MTD of atezolizumab was not reached and no dose-limiting toxicities (DLTs) were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight-based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

The dose and schedule for CIS and GEM in the PEGPH20 in combination with CIS and GEM (PEGCISGEM) and PEGPH20 in combination with CIS, GEM, and atezolizumab (PEGCISGEMATEZO) treatment arms of the study are per a Phase 3 trial conducted in biliary tract cancers, the ABC-02 trial (Valle 2010), with the exception that the first doses of CIS and GEM will be given on Day 2 instead of Day 1 and second doses of CIS and GEM will be given on Day 9 instead of Day 8. This is based on preclinical data indicating that maximum depletion of tumor levels of HA occurs by 24 hours after a dose of PEGPH20, potentially making tumors more responsive to the cytotoxic effects of chemotherapy.

In the Control arm the dose and schedule for CIS and GEM are also per the ABC-02 trial (Valle 2010) with CIS and GEM being administered on Day 1 and Day 8 of each 21-day cycle.

Since PEGPH20 has not been evaluated in clinical studies in combination with atezolizumab, the study will have a Run-in portion with PEGCISGEM and PEGCISGEMATEZO treatments to evaluate the safety and tolerability of PEGPH20 (at a dose of 3.0 µg/kg) in combination with GEM, CIS, and subsequently GEM, CIS, and Atezolizumab, before the randomized Expansion portion is initiated.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Study Objectives

Note: The objectives described below will be evaluated in subjects with previously untreated unresectable, locally advanced, or metastatic ICC, ECC, and gallbladder adenocarcinoma.

Run-in Portion

Primary:

- To assess the safety and tolerability of (1) PEGCISGEM and (2) PEGCISGEMATEZO

Secondary:

- To assess the PK of PEGPH20, CIS, GEM, and atezolizumab when given in combination
- To obtain an early assessment of the antitumor activity of PEGCISGEM and PEGCISGEMATEZO, as assessed by ORR based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Exploratory:

- To characterize changes in cancer antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) from baseline
- To obtain an early assessment of the antitumor activity of PEGCISGEMATEZO, as assessed by ORR based on Immune-Modified Response Evaluation Criteria (Immune-Modified RECIST)
- To obtain an early assessment of the antitumor activity of PEGCISGEM and PEGCISGEMATEZO, as assessed by DOR and PFS based on RECIST v1.1, and OS
- To assess the treatment effect of PEGCISGEM and PEGCISGEMATEZO on plasma HA levels and potential biomarkers and correlate those effects with clinical outcome
- To assess the prognostic and/or predictive value of exploratory biomarkers

Expansion Portion

Primary:

- To evaluate the efficacy of PEGCISGEMATEZO and PEGCISGEM compared with CISGEM, as assessed by ORR based on RECIST v1.1

Secondary:

- To evaluate the efficacy of PEGCISGEMATEZO and PEGCISGEM compared with CISGEM, as assessed by DOR, disease control rate (DCR; complete response [CR] + partial response [PR] + stable disease [SD]), and PFS based on RECIST v1.1, and OS
- To evaluate the efficacy of PEGCISGEMATEZO and PEGCISGEM compared with CISGEM, as assessed by ORR, DOR, PFS based on RECIST v1.1 and OS in subjects by PD-L1 expression levels
- To characterize the PK of PEGPH20, CIS, GEM, and atezolizumab when given in combination
- To characterize the PK of PEGPH20, CIS, and GEM when given in combination
- To evaluate the safety and tolerability profile of PEGCISGEM and PEGCISGEMATEZO compared with CISGEM

Exploratory:

- To evaluate the efficacy of PEGCISGEMATEZO based on Immune-Modified RECIST, as assessed by ORR and DOR
- To evaluate the efficacy of PEGCISGEMATEZO, as assessed by ORR and DOR based on Immune-Modified RECIST in subjects by PD-L1 expression levels
- To evaluate the DCR of PEGCISGEMATEZO according to Immune-Modified RECIST
- To assess the treatment effect of PEGCISGEM, PEGCISGEMATEZO and CISGEM on plasma HA levels and potential biomarkers and correlate those effects with clinical outcome
- To assess the prognostic and/or predictive value of exploratory biomarkers
- To characterize changes in CA19-9 and CEA from baseline

5.2. Study Endpoints

Run-in portion

Primary:

- Incidence of AEs, changes in clinical safety laboratory values, changes in cardiovascular parameters (electrocardiogram [ECG]), vital signs, and dose modifications (e.g., dose interruptions and delays)

Secondary:

- PK parameters of PEGPH20: maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), elimination rate constant (k_{el}), $t_{1/2}$, clearance (CL), volume of distribution (V_d), and area-under-the-concentration time curve (AUC).
- PK parameters of atezolizumab: C_{max}, C_{min}, $t_{1/2}$, AUC, V_d, and CL when applicable
- PK parameters for GEM: C_{max}, $t_{1/2}$, AUC, V_d, and CL when applicable
- PK parameters for CIS (total and unbound): C_{max}, $t_{1/2}$, AUC, V_d, and CL when applicable
- ORR based on RECIST v1.1

Exploratory:

- Change in CA19-9 from baseline
- Change in CEA from baseline
- ORR based on Immune-Modified RECIST
- DOR and PFS based on RECIST v1.1
- OS
- Changes in plasma HA from baseline
- Changes in tumor HA from baseline when available
- Explore co-variates of safety and efficacy parameters with drug exposure, as measured by plasma HA levels
- Explore co-variates of safety and efficacy parameters with exploratory biomarker responses

Expansion portion

Primary:

- ORR based on RECIST v1.1

Secondary:

- DOR, PFS, and DCR based on RECIST v1.1, and OS
- ORR, DOR, and PFS based on RECIST v1.1, and OS by PD-L1 expression levels
- PK parameters of PEGPH20: C_{max}, C_{min}, k_{el}, $t_{1/2}$, CL, V_d, and AUC
- PK parameters of atezolizumab: C_{max}, C_{min}, $t_{1/2}$, AUC, V_d, and CL when applicable
- PK parameters of GEM and CIS (bound and free): C_{max}, $t_{1/2}$, AUC, V_d, and CL when applicable
- Incidence of AEs, changes in clinical safety laboratory values, changes in ECG, vital signs, and dose modifications (e.g., dose interruptions and delays)

Exploratory:

- ORR and DOR based on Immune-Modified RECIST
- ORR and DOR based on Immune-Modified RECIST by PD-L1 expression levels
- DCR, as assessed by the Investigator according to Immune-Modified RECIST
- Changes in plasma HA from baseline
- Changes in tumor HA from baseline, when available
- Explore co-variates of safety and efficacy parameters with drug exposure as measured by plasma HA levels
- Explore co-variates of safety and efficacy parameters with exploratory biomarker responses
- Change in CA19-9 from baseline
- Change in CEA from baseline

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan: Description

This is a Phase 1b, multicenter, randomized, open-label, study of PEGCISGEM and PEGCISGEMATEZO treatments compared with CISGEM treatment in previously untreated subjects with unresectable, locally advanced or metastatic ICC, ECC, and gallbladder adenocarcinoma.

The study will have a Run-in portion and an Expansion portion.

The Run-in portion will be used to evaluate the safety profile of the PEGCISGEM and PEGCISGEMATEZO treatments prior to evaluating the efficacy and safety of PEGCISGEM and

PEGCISGEMATEZO treatments compared with CISGEM treatment in the Expansion portion of the study. The study design is depicted in Figure 1.

Effective with Protocol Amendment 2, all-comers (subjects unselected for tumor HA and PD-L1 expression levels) will be enrolled in the study and subjects' tumor samples will be tested retrospectively for HA and PD-L1 expression levels.

In the Run-in portion, approximately 6 subjects will be enrolled in the PEGCISGEM arm and undergo at least 1 treatment cycle; thereafter, approximately 6 subjects will be enrolled in the PEGCISGEMATEZO arm. An additional 8 subjects may be enrolled in the Run-in portion to further assess the tolerability of PEGPH20 in either combination arm in order to establish an acceptable safety profile prior to the Expansion portion of the study.

After the Run-in portion of the study, the Expansion portion will begin. A total of approximately 65 subjects will be enrolled in the Expansion portion including approximately 50 subjects per Protocol Amendment 2 and approximately 15 additional subjects per Protocol Amendment 3.

The treatment period will consist of 21-day cycles in both the Run-in and Expansion portions of the study.

PEGPH20 will be administered at 3.0 µg/kg once weekly during Weeks 1-3 of all cycles in both portions of the study. An additional cohort of approximately 15 subjects will be enrolled in the Expansion portion under Protocol Amendment 3 who will receive PEGCISGEMATEZO, with PEGPH20 3.0 µg/kg administered twice weekly in Cycle 1 and once weekly in subsequent cycles (Table 7), to evaluate the efficacy and safety of the PEGCISGEMATEZO combination treatment at a higher PEGPH20 dosing frequency.

The dosing schedule for atezolizumab administration in the Run-in portion will be the same as for subjects in the Expansion portion with 1200 mg atezolizumab administered 1 to 3 hours after PEGPH20 on Day 1 of each 21-day cycle in subjects receiving PEGCISGEMATEZO treatment.

The dosing schedule for CIS and GEM administration in subjects receiving PEGCISGEM and PEGCISGEMATEZO treatment in the Run-in portion will be the same as for subjects in the Expansion portion with 25 mg/m^2 of CIS and 1000 mg/m^2 of GEM administered on Day 2 and Day 9 of each cycle.

In the CISGEM control arm, the dosing schedule for CIS and GEM administration will be 25 mg/m^2 of CIS and 1000 mg/m^2 of GEM administered on Day 1 and Day 8 of each treatment cycle in Expansion portion.

Treatment in both portions of the study will continue until death, withdrawal of consent from the study, disease progression, or unacceptable toxicity (additional details in Section 6.1.3). Radiographic disease response/progression will be evaluated using RECIST v1.1 (see Section 8.2.15 for details on imaging/radiologic evaluation and Appendix B for details on RECIST v1.1). In addition, radiographic disease response/progression in subjects receiving PEGCISGEMATEZO will also be evaluated using Immune-Modified RECIST (refer to Appendix D for further details on Immune-Modified RECIST) due to the possibility of pseudoprogression (an initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response with atezolizumab treatment). In the absence of unacceptable toxicity, subjects who meet criteria for disease progression per RECIST v1.1 while receiving atezolizumab will be permitted to continue treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the Investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Subject's written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial disease progression

Dose modifications for chemotherapy are permitted in the Run-in portion and Expansion portion of the study. Dose interruptions are allowed for atezolizumab in both the Run-in portion and Expansion portion of the study. No dose modifications of atezolizumab are allowed in this study. PEGPH20 dose interruption and dose reductions are allowed in both portions of the study. Dose reduction of PEGPH20 to lower doses of 2.2 µg/kg and 1.6 µg/kg will be recommended if necessary based on toxicities in the Run-in portion and the Expansion portion. After dose reduction, the dose of PEGPH20 may be re-escalated to the prior dose utilized, at the Investigator's discretion, following a discussion with the Sponsor, provided there are no safety concerns. Dose modification guidelines are provided in Section 8.3 for PEGPH20, CIS and GEM. Guidance on atezolizumab dose interruption and discontinuation due to AEs are provided in the atezolizumab Investigator's Brochure. Guidance on the allowed dose reduction levels for PEGPH20 are provided in Section 8.3.1.3. Additional dose modification guidelines for CIS and GEM are provided in the Prescribing Information of these chemotherapeutic agents.

In single-agent studies of PEGPH20 and in a Phase 1 combination study of PEGPH20 with GEM, the DLTs were MSEs 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 (HALO-110-101) uses an immunotherapeutic agent (atezolizumab) and dexamethasone and other steroids may suppress an immune response, steroids should only be used to treat AEs in some exceptional circumstances or at the Investigator's discretion as detailed in Section 10.12.3.

PEGPH20 and atezolizumab administration must be held if steroids are administered to treat AEs and can only be restarted once the steroid is discontinued. The only exceptions are topical, inhaled, intranasal or intra-articular steroids, thyroid-replacement hormone, and mineralocorticoids, which are allowed as described in Section 7.2 and Section 10.12.3, and low-dose steroids as described in Section 10.12.3.

In addition to study medication, all subjects in the PEGCISGEM and PEGCISGEMATEZO arms will also be administered piroxicam to reduce potential musculoskeletal symptoms often associated with PEGPH20 administration. Piroxicam (20 mg) will be administered at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. A non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce

potential MSEs, at the discretion of the Investigator. 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, OTC drugs and physical therapy can also be used at the Investigator's discretion.

To decrease the risk of TE events, an identified risk of PEGPH20, and based on the incidence of TE events observed in this study to date, prophylactic enoxaparin will be administered subcutaneously at 1 mg/kg/day to all subjects receiving PEGPH20 including subjects in the PEGCISGEM and PEGCISGEMATEZO arms enrolled through Protocol Amendment 2 and the additional cohort of 15 subjects enrolled under Protocol Amendment 3 receiving PEGCISGEMATEZO (details in Section 10.1.1). The dosage of enoxaparin of 1 mg/kg/day is the same as that administered in trials of PEGPH20 in combination with GEM and NAB in PDA (completed Study HALO-109-202 and ongoing Study HALO-109-301).

If enoxaparin is discontinued for any reason in subjects receiving PEGPH20, PEGPH20 will also be discontinued. Treatment with other drugs, however, may continue at the Investigator's discretion.

Subjects who discontinue treatment with all study drugs (PEGCISGEM/PEGCISGEMATEZO/CISGEM) will have an End of Treatment Visit and enter long-term follow-up for survival.

Subjects will be assessed for AEs and clinical laboratory evaluations as graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03.

An independent DMC will periodically review safety data to protect subject welfare and identify potential safety signals in the Run-in and Expansion portions of the study.

In both portions of the study, tumor response will be assessed by a local reviewer after every 3 cycles based on RECIST v1.1 criteria and Immune-Modified RECIST. Scans for RECIST v1.1 and Immune-Modified RECIST may be obtained any time on or after Day 15 to allow enough time for the scan to be reviewed locally prior to the subject's next scheduled dosing visit.

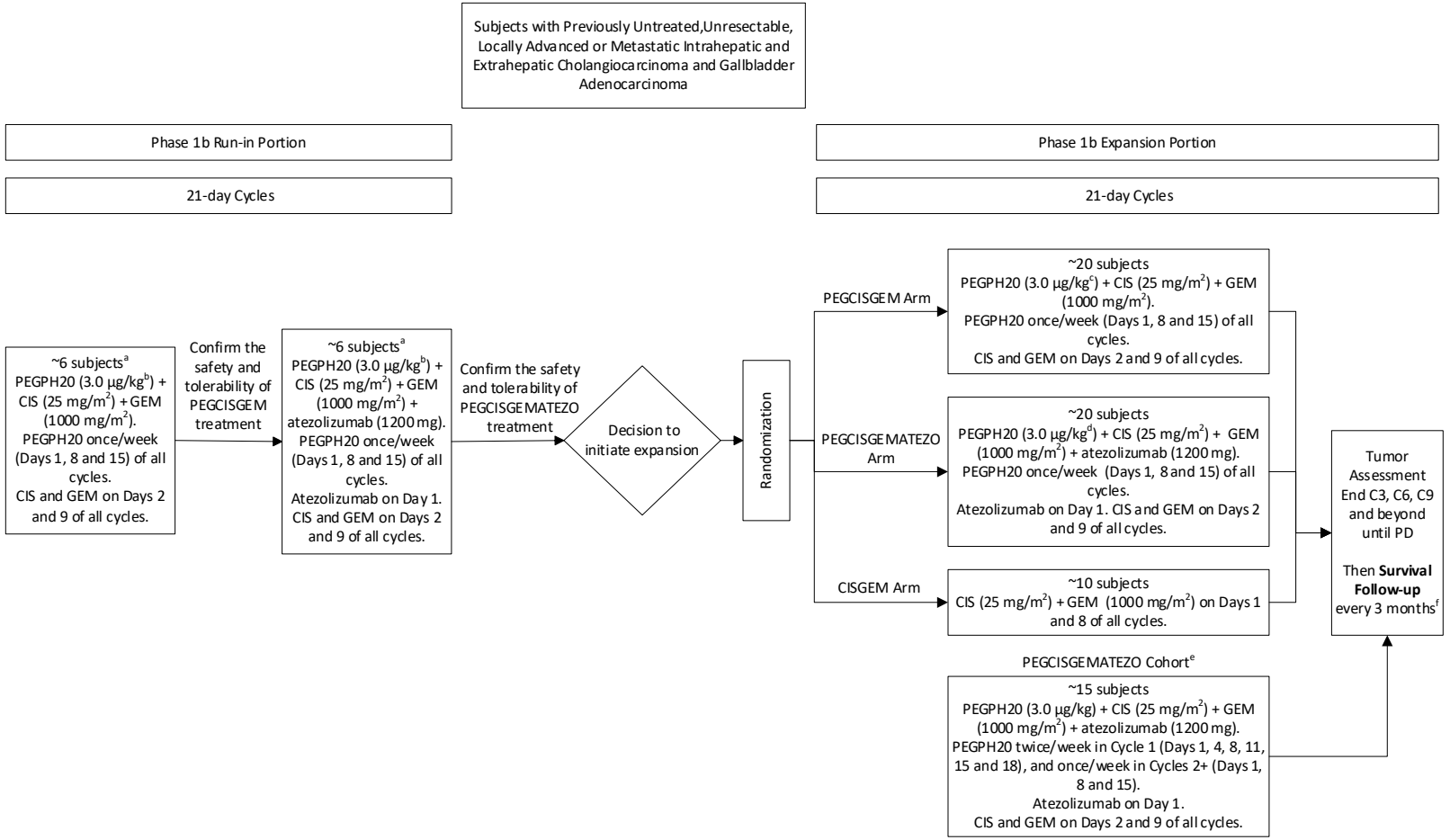
A confirmatory scan is required in both portions of the study for subjects with CR or PR for confirmation of response. This confirmatory scan may be performed at the earliest 28 days after the date of the first documented response (per RECIST v1.1) (preferred) or at the next scheduled imaging timepoint, whichever is clinically indicated (details in Section 8.2.15).

A confirmatory scan is also required for subjects receiving PEGCISGEMATEZO to confirm radiological disease progression, per Immune-Modified RECIST. This confirmatory scan should be obtained no sooner than 28 days after the initial scan that showed progression (this can be the next scheduled tumor assessment scan).

All scans for tumor assessments performed during the study should be archived in accordance with the standard local practice. The scans will be submitted to a central imaging vendor (CIV) selected by the Sponsor for potential central review at a later time.

After the End of Treatment Visit, subjects will enter long-term follow-up during which information on the subject's survival and subsequent anticancer therapy will be obtained by the site every 12 weeks until the subject dies, is lost to follow-up, or withdraws consent. Subjects may be contacted more frequently to collect information on survival and subsequent anticancer therapy, as required, prior to important study timepoints, including DMC meetings and database locks.

Figure 1: Study Design - Phase 1b Run-in and Expansion (HALO-110-101)



Abbreviations: CIS = cisplatin; GEM = gemcitabine; PEGPH20 = PEGylated recombinant human hyaluronidase;

[a] An additional 8 subjects may be enrolled in the Run-in portion to further assess the tolerability of either combination arm with PEGPH20 in order to establish an acceptable safety profile prior to the Expansion portion of the study.

[b] Dose reduction of PEGPH20 to lower doses of 2.2 µg/kg and 1.6 µg/kg will be recommended if necessary based on toxicities.

[c] The highest PEGPH20 dose level found to be safe and tolerable in PEGCISGEM arm of the Run-in portion will be utilized in the PEGCISGEM arm of the Dose Expansion portion.

[d] The highest PEGPH20 dose level found to be safe and tolerable in PEGCISGEMATEZO arm of the Run-in portion will be utilized in the PEGCISGEMATEZO arm of the Dose Expansion portion.
[e] Per Protocol Amendment 3.
[f] Subjects may be contacted more frequently to collect information on survival and subsequent anticancer therapy, as required, prior to important study timepoints, including DMC meetings and database locks.

6.1.1. Phase 1b Run-in

In the Run-in portion, approximately 6 subjects will receive 3.0 µg/kg PEGPH20 on Day 1, Day 8, and Day 15 and 25 mg/m^2 of CIS and 1000 mg/m^2 of GEM administered on Day 2 and Day 9 of each 21-day cycle.

After the 6 subjects are treated for at least 1 cycle without significant toxicities, the PEGCISGEMATEZO arm will open and subjects in this arm will receive 3.0 µg/kg PEGPH20 on Day 1, Day 8, and Day 15 in combination with 1200 mg atezolizumab on Day 1 and 25 mg/m^2 of CIS and 1000 mg/m^2 of GEM administered on Day 2 and Day 9 of each 21-day cycle.

PEGPH20 dose reduction to a lower dose of 2.2 µg/kg or 1.6 µg/kg will be performed if necessary.

An additional 8 subjects may be enrolled in the Run-in portion to further assess the tolerability of either combination arm with PEGPH20 in order to establish an acceptable safety profile prior to the Expansion portion of the study.

The Sponsor in collaboration with the treating investigators will review all available safety data from all subjects in the Run-in portion, and the Sponsor will determine if the doses/tolerability profile is acceptable.

DLT evaluation of PEGCISGEM or PEGCISGEMATEZO treatments at a given PEGPH20 dose level will be carried out during DLT evaluation period (i.e., Cycle 1) as follows:

Initially 3 subjects will be enrolled:

- If ≤1 subjects experiences a DLT then 3 additional subjects will be enrolled.
  - If ≤1 subject experiences a DLT among the 6 enrolled subjects then the combination evaluated (PEGCISGEM or PEGCISGEMATEZO) will be considered safe.
  - If ≥2 subjects experience DLTs then PEGPH20 dose will be de-escalated to the next lower dose level (see Table 6) and additional subjects (up to a total of 6) will be enrolled and evaluated.
- If ≥2 subjects experience a DLT, then PEGPH20 dose will be de-escalated to the next lower dose level and additional subjects (up to a total of 6) will be enrolled and evaluated.
- If the combination of PEGCISGEM is found to be safe and tolerable, the PEGCISGEMATEZO arm will be opened at the same PEGPH20 dose level found to be safe and tolerable in the PEGCISGEM arm, and the tolerability of this combination will be evaluated following the steps outlined earlier.
- The highest PEGPH20 dose level found to be safe and tolerable in PEGCISGEM arm of the Run-in portion will be utilized in the PEGCISGEM arm of the Dose Expansion portion. The highest PEGPH20 dose level found to be safe and tolerable in PEGCISGEMATEZO arm of the Run-in portion will be utilized in the PEGCISGEMATEZO arm of the Dose Expansion portion.

- Subjects who drop out during the initial 21 days of treatment without experiencing a DLT will be replaced.
- Safety evaluation will be initiated at PEGPH20 3.0 µg/kg dose level for the PEGCISGEM combination.
- Subjects who experience DLTs during Cycle 1 will be permanently discontinued from all study treatments.

Table 6: Dose Allocation and Cohort Schedule - Run-in Portion (PEGCISGEM and PEGCISGEMATEZO treatments)

Cohort	PEGPH20 µg/kg	CIS mg/m^2	GEM mg/m^2	ATEZOLIZUMAB mg
-2	1.6	25	1000	1200
-1	2.2	25	1000	1200
1	3.0	25	1000	1200

Abbreviations: PEGPH20 = PEGylated recombinant human hyaluronidase; CIS = cisplatin; GEM = gemcitabine
Note: Each treatment cycle is 21 days. Dose interruption and modifications are permitted (See Section 8.3 for further details).

Definition of DLT

Treatment-related AEs that limit the dose of PEGPH20 or the combination (PEGCISGEM/PEGCISGEMATEZO) may be considered as DLTs. 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:

- Treatment-emergent Grade ≥3 toxicity that is considered related to either PEGPH20 or the combination (PEGCISGEM/PEGCISGEMATEZO)
  - MSEs, colitis, and immune-related toxicities, infections will be considered as DLTs only if they reach Grade ≥3 severity despite adequate supportive care measures.
  - Grade 3 nausea, vomiting, and diarrhea will be considered as DLTs if they persist for >72 hours despite optimal supportive care.
  - Grade 4 nausea, vomiting, and diarrhea will be considered as DLTs if they reach Grade 4 severity despite optimal supportive care, irrespective of duration.
- Treatment-emergent Grade ≥3 symptomatic hepatic toxicity that is considered related to either PEGPH20 or the combination that does not resolve to Grade ≤2 within 48 hours or Grade ≥3 asymptomatic hepatic toxicity that is considered related to either PEGPH20 or the combination that does not resolve to Grade ≤1 within 3 weeks of onset with the following exception:
  - For patients with Grade 2 alkaline phosphatase abnormality at baseline, an increase to >8 × the upper limit of normal (ULN) that does not resolve to Grade ≤2 within 48 hours (if symptomatic) or that does not resolve to Grade ≤1 within 3 weeks of onset (if asymptomatic) will be considered a DLT.
- Grade 4 hepatic toxicity of any duration will be considered as a DLT.

- Grade ≥3 non-hematologic, non-hepatic organ toxicity, excluding the following:
  - Grade 3 immune-related AE that resolves to Grade ≤1 with immunosuppressant therapy within 3 weeks of its onset
  - Grade 3 autoimmune thyroiditis or other endocrine abnormality that can be managed by endocrine therapy or hormonal replacement
- Grade 3 neutropenia (asymptomatic) will not be considered a DLT; however Grade 4 neutropenia lasting 7 days or longer will be considered a DLT.
- Febrile neutropenia (defined below) will be considered as a DLT.

  Febrile Neutropenia - Fever is present, defined as an oral temperature of at least 38.0°C on at least 2 occasions within 24 hours, or a single oral temperature of at least 38.3°C, in the presence of neutropenia, defined as an absolute neutrophil count (ANC) of less than 500 cells/µl. Fever may also be defined as a rectal temperature of 38.6°C on at least 2 occasions within 24 hours, or a single rectal temperature of 39°C (FDA Guidance for Industry: Empiric Therapy of Febrile Neutropenia - Developing Antimicrobial Drugs for Treatment 1998).
- 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 the combination dosing (PEGCISGEM/PEGCISGEMATEZO) 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 in the PEGCISGEM arm must receive 1 of the 3 full planned doses of PEGPH20 and 1 complete dose each of CIS and GEM in Cycle 1.

To be considered evaluable for DLT assessment, subjects in the PEGCISGEMATEZO arm must receive 1 of the 3 full planned doses of PEGPH20 and 1 complete dose each of atezolizumab, CIS, and GEM in Cycle 1.

Subjects who experience a DLT within the first 21 days of treatment and withdraw from the study treatment 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. Subjects who experience DLTs in the Run-in portion will be permanently discontinued from all study treatments.

6.1.2. Phase 1b Dose Expansion

Approximately 50 previously untreated subjects will be randomized in a 2:2:1 ratio into 1 of 3 treatment arms as follows:

- PEGCISGEM arm: PEGPH20 (3.0 µg/kg) + CIS (25 mg/m^2) + GEM (1000 mg/m^2)
- PEGCISGEMATEZO arm: PEGPH20 (3.0 µg/kg) + atezolizumab (1200 mg) + CIS (25 mg/m^2) + GEM (1000 mg/m^2)
- CISGEM (control) arm: CIS (25 mg/m^2) + GEM (1000 mg/m^2)

Randomization will be stratified by geographical region (North America and Asia) and cancer type (cholangiocarcinoma and gallbladder).

An additional cohort of approximately 15 subjects will be enrolled in the Expansion portion under Protocol Amendment 3 and receive PEGCISGEMATEZO treatment: PEGPH20 (3.0 µg/kg) + Atezolizumab (1200 mg) + CIS (25 mg/m^2) + GEM (1000 mg/m^2).

The study medication dosing and treatment schedule are shown in Table 7.

Table 7: Study Medication Dosing and Treatment Schedule

Timepoint	**PEGCISGEM Treatment**
All cycles (21-day cycles)	
Week 1	
Day 1	PEGPH20
Day 2	CIS + GEM (24 ± 4 hours after Day 1 dose of PEGPH20)
Week 2	
Day 8	PEGPH20
Day 9	CIS + GEM (24 ± 4 hours after Day 8 dose of PEGPH20)
Week 3	
Day 15	PEGPH20
Timepoint	**PEGCISGEMATEZO Treatment**
Cycle 1 (21-day cycles)	
Week 1	
Day 1	PEGPH20 Atezolizumab (1 to 3 hours after PEGPH20)
Day 2	CIS + GEM (24 ± 4 hours after Day 1 dose of PEGPH20)
Day 4[a]	PEGPH20
Week 2	
Day 8	PEGPH20
Day 9	CIS + GEM (24 ± 4 hours after Day 8 dose of PEGPH20)
Day 11[a]	PEGPH20
Week 3	
Day 15	PEGPH20
Day 18[a]	PEGPH20

Table 7: Study Medication Dosing and Treatment Schedule (Continued)

Cycle 2 and Beyond	
Week 1	
Day 1	PEGPH20 Atezolizumab (1 to 3 hours after PEGPH20)
Day 2	CIS + GEM (24 ± 4 hours after Day 1 dose of PEGPH20)
Week 2	
Day 8	PEGPH20
Day 9	CIS + GEM (24 ± 4 hours after Day 8 dose of PEGPH20)
Week 3	
Day 15	PEGPH20
Timepoint	**CISGEM Treatment**
All cycles (21-day cycles)	
Week 1	
Day 1	CIS + GEM
Week 2	
Day 8	CIS + GEM

Abbreviations: PEGPH20 = PEGylated recombinant human hyaluronidase; GEM = gemcitabine; CIS = cisplatin
Note: Dose interruption and modifications are permitted (See Section 8.3 for further details).
[a] This visit is applicable to the ~15 subjects enrolled under Protocol Amendment 3 only.

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 radiologic disease progression or clinical progression or unacceptable toxicity is documented.

Due to the possibility of "pseudoprogression" in immunotherapy trials, subjects who meet the criteria for disease progression, per RECIST v1.1, while receiving atezolizumab will be permitted to continue treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in ECOG Performance Status that can be attributed to disease progression

- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Subject's written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial 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 all study drugs will be followed every 12 weeks for survival until death, withdrawal of consent, or lost to follow-up. Subjects may be contacted more frequently to collect information on survival and subsequent anticancer therapy, as required, prior to important study timepoints, including DMC meetings and database locks.

6.1.4. Disease Progression

Disease progression will be defined by the presence of the following, based on the Investigator's radiology reviewer's assessment:

- Disease progression documented by CT scan/Magnetic resonance imaging (MRI) scan based on RECIST v1.1 (Appendix B)
- Per Immune-Modified RECIST, disease progression for subjects receiving PEGCISGEMATEZO requires confirmation of progression with an additional scan obtained no sooner than 28 days after the initial scan that showed progression based on RECIST v1.1.

Radiographic disease progression is based on the analysis of CT/MRI scans by the Investigator. Investigators should continue study treatment until disease progression (as defined above and described in Section 6.1) 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 all study drugs will be followed every 12 weeks for survival until death, withdrawal of consent, or lost to follow-up. Subjects may be contacted more frequently to collect information on survival and subsequent anticancer therapy, as required, prior to important study timepoints, including DMC meetings and database locks.

7. SELECTION AND WITHDRAWAL OF SUBJECTS AND STUDY TERMINATION

Males and females aged 18 years and older with previously untreated, locally advanced or metastatic ICC, ECC, and gallbladder adenocarcinoma who meet the inclusion/exclusion criteria will be enrolled in both portions of the study.

7.1. Inclusion Criteria

For both portions of the study, 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 (ICF), signed by subject or legally authorized representative.
2. Subjects must be determined to have histologically confirmed unresectable, locally advanced or metastatic adenocarcinoma of the intra- and/or extra-hepatic bile ducts and/or gallbladder. Prior to enrollment, confirmation of shipment of tissue sample to the central laboratory must be obtained. Subjects must have sufficient tissue with architectural integrity, including tumor and associated stroma, available for retrospective PD-L1 and HA testing (details will be included in a separate Laboratory Manual).

   Note: Tumor biopsies must be collected on or after the date that locally advanced or metastatic disease is documented.
3. One or more lesions measurable on CT scan/MRI scan per RECIST v1.1.
4. Subjects having ECOG Performance Status of 0 to 1.
5. Life expectancy ≥3 months.
6. Males and females aged ≥18 years.
7. Screening clinical laboratory values as follows:
   - Total bilirubin ≤1.5 × ULN, except for Gilbert's syndrome
   - Aspartate aminotransferase and alanine aminotransferase ≤2.5 × ULN (<5 × ULN is allowed if liver metastases or liver involvement are present)
   - Serum creatinine ≤1.5 mg/dL
   - Serum albumin ≥2.5 g/dL
   - Hemoglobin ≥9 g/dL (transfusion and erythropoietic agents allowed)
   - Absolute neutrophil count ≥1500 cells/mm^3
   - Platelet count ≥100,000/mm^3
8. 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).
9. For WOCBP and for men, agreement to use a highly effective contraceptive method from the time of screening throughout the study until 5 months (WOCBP) or 6 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, barrier methods, and/or true sexual abstinence.

7.2. Exclusion Criteria

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

1. Clinical evidence of deep vein thrombosis or pulmonary embolism present during the screening period.
   - Subject with superficial vein thrombosis are eligible.

- Subjects with visceral/splanchnic vein thrombosis, that in the opinion of the Principal Investigator are primarily associated with the anatomic location of the underlying disease of metastatic biliary tract cancer, are eligible.

2. New York Heart Association Class III or IV (Appendix C) cardiac disease, atrial fibrillation, unstable angina, or myocardial infarction within the past 12 months before screening.
3. Subjects with known brain metastases
4. History of cerebrovascular accident or transient ischemic attack
5. History of active bleeding within the last 3 months prior to screening requiring transfusion.
6. Contraindication to heparin as per institutional guidelines.
7. Subjects must have received no previous radiotherapy, surgery, chemotherapy or investigational therapy for treatment of metastatic or locally advanced disease.
8. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), anti-programmed cell death protein 1 (anti-PD-1), and anti-PD-L1 therapeutic antibodies
9. Prior treatment with 5-fluorouracil (FU) or GEM administered as a radiation sensitizer in the neoadjuvant and adjuvant settings surrounding surgery, during and up to 4 weeks after radiation therapy, is allowed if all toxicities have returned to baseline or ≤ Grade 1.
10. If a subject received therapy in the adjuvant setting, tumor recurrence or disease progression must have occurred no sooner than 6 months after completing the last dose of the adjuvant therapy.
11. Clinically significant pre-existing carotid artery disease.
12. Active, uncontrolled bacterial, viral, or fungal infection requiring systemic therapy.
13. Known allergy to hyaluronidase.
14. Intolerance to NSAIDs.
15. Current use of megestrol acetate or megestrol acetate-containing drugs (within 10 days of Day 1).
16. Women currently pregnant or breastfeeding.
17. Positive human immunodeficiency virus (HIV) test
18. Active hepatitis B virus (HBV) infection, defined as having a positive hepatitis B surface antigen (HBsAg) test at screening
    - Subjects with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study if active HBV infection is ruled out on the basis of HBV ribonucleic acid (RNA)/deoxyribonucleic acid (DNA) viral load per local guidelines.
19. Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test at screening

- Subjects who have a positive HCV antibody test are eligible for the study if a polymerase chain reaction assay is negative for HCV RNA.

20. Active tuberculosis.
21. History of:
    a. Idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
    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.
22. Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, fatty liver, and inherited liver disease.
23. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells.
24. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
25. Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
    - Subjects receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
26. Signs or symptoms of infection within 2 weeks prior to initiation of study treatment.
27. Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study
    - Placement of central venous access catheter(s) (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.
28. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study
    - Influenza vaccination should be given during influenza season only (approximately October to March in the Northern Hemisphere and approximately April through September in the Southern Hemisphere). Subjects must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to the start of study treatment, during treatment, or within 5 months after the last dose of atezolizumab.

29. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2) within 6 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment.
30. Treatment with systemic immunosuppressive medication (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor alpha [anti-TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study
    - Subjects who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.
    - The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for subjects with orthostatic hypotension, chronic obstructive pulmonary disease, or adrenocortical insufficiency is allowed.
    - Subjects with a history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumor assessments performed using MRI.
31. Active or history of autoimmune disease, including, but not limited to, colitis, Crohn's disease, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.*
    - Subjects with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study after discussion with and approval by the Medical Monitor.
    - Subjects with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study after discussion with and approval by the Medical Monitor.
32. Subjects with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., subjects with psoriatic arthritis) are permitted provided that they meet the following conditions:
    - Subjects with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
    - Rash must cover less than 10% of body surface area (BSA)
    - Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, fluocinolone 0.01%, desonide 0.05%, alclometasone dipropionate 0.05%)
    - No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)

33. Uncontrolled tumor-related pain
    - Subjects requiring narcotic pain medication must be on a stable regimen at study entry.
    - Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to start of study treatment. Subjects should be recovered from the effects of radiation. There is no required minimum recovery period.
    - Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to the start of study treatment.
34. Uncontrolled hypercalcemia (>1.5 mmol/L ionized calcium or calcium >12 mg/dL or corrected serum calcium >ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy (unless bisphosphonate is used to prevent skeletal events).
35. Prior allogeneic stem cell or solid organ transplantation.
36. 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.
37. 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.
38. 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 and/or begins breast feeding (treatment must be discontinued immediately).
- Subjects for whom enoxaparin is discontinued for any reason (PEGPH20 will be discontinued if administered, treatment with other study drugs may continue as deemed appropriate by the Investigator).

Subjects who discontinue treatment with all study drugs 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, CIS, GEM, and atezolizumab [if applicable] treatments), the subject will enter long-term follow-up for assessment of survival and subsequent anti-cancer therapies (Section 8.1.2.5). 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.
- DLT during the Run-in portion of the study.
- Adverse event.
- 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/BSA, and CT/MRI scan.

Note: Plasma samples are required for PEGPH20 PK, CIS PK, GEM PK, HA, biomarker, and PEGPH20 immunogenicity analysis. Serum samples are required for atezolizumab PK, atezolizumab immunogenicity, CA19-9, and CEA 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 ICF.
- Review inclusion/exclusion criteria.
- Collect medical and prior medication history.
- Collect history of bile duct adenocarcinoma (intrahepatic, extrahepatic, and gallbladder).
- Confirm availability of and retrieve tumor tissue (refer to Inclusion Criterion #2 for more details). Tumor tissue must be sent to central laboratory for retrospective testing of HA levels.

- Obtain CT/MRI scan (baseline scan) for disease assessment and eligibility review by a local reviewer and send to CIV for storage. In addition, chest CT scans should be read locally to evaluate for the presence of PE. If subject has signs or symptoms of PE after the initial scan was completed, the chest scan should be repeated prior to enrollment (in Run-in)/randomization (in Expansion) to assess for the presence of PE. If a PE is present, the subject will not be enrolled/randomized.
- Obtain Doppler ultrasound of lower extremities.
- Perform the following assessments: 12-lead ECG, physical examination, vital signs, ECOG Performance Status, height and weight/BSA within 28 days before Day 1 (first dose of study medication), and urine or serum pregnancy test within 7 days before Day 1 (WOCBP; local laboratory).
- Obtain samples for the following tests and send to the central laboratory: CA19-9 and CEA analysis, plasma HA levels and exploratory biomarkers, thyroid hormones, hematology, blood chemistry, coagulation, viral serology, and urinalysis.
- Register subjects into an Interactive Web Response System (IWRS) for screening.
- Enroll subjects (and randomize if in Expansion portion).

8.1.2. Treatment Period

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

Note: Hydration and electrolyte supplementation with potassium and magnesium must be given prior to CIS infusion per individual institutional standards. Premedication with antiemetics will be administered as standard-of-care to all subjects prior to chemotherapy (CIS and GEM) infusion. The use of steroids during treatment in the study should be avoided unless emesis is not controlled with other antiemetics.

Also note that the translational medicine and PK samples are not listed below and should be obtained at the timepoints mentioned in Table 4 for subjects receiving PEGCISGEM and PEGCISGEMATEZO treatment and in Table 5 for subjects receiving CISGEM treatment in both portions of the study.

8.1.2.1. Subjects Receiving PEGCISGEM Treatment (Run-in and Expansion)

8.1.2.1.1. Treatment Cycle 1

8.1.2.1.1.1. Cycle 1 Day 1

Before PEGPH20 Infusion

- Confirm subjects' eligibility based on inclusion and exclusion criteria.
- Perform physical examination.
- Perform the following assessments: vital signs, ECOG Performance Status, and weight/BSA.
  - Obtain samples for the following tests and send to the central laboratory: hematology, blood chemistry, and urinalysis.
- Obtain samples for PEGPH20 immunogenicity testing and send to the central laboratory.
- Obtain samples for CA19-9 and CEA testing and send to the central laboratory.
- Administer piroxicam (20 mg) at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. Note: A non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

PEGPH20 Infusion

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

8.1.2.1.1.2. Cycle 1 Day 9

Before CIS and GEM Infusion

- Assess vital signs.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

CIS and GEM Infusion

- CIS IV infusion over 1 hour, 24 hours (±4 hours) after completion of PEGPH20 infusion.
- GEM IV infusion over 30 minutes, 24 hours (±4 hours) after completion of PEGPH20 infusion.

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

8.1.2.1.2.1. Cycle 2 and Beyond Day 1

Before PEGPH20 Infusion

- Perform urine/serum pregnancy test (WOCBP) at a local laboratory.
- Perform physical examination.
- Perform the following assessments: vital signs, ECOG Performance Status, and weight/BSA.
- Obtain samples for the following tests and send to the central laboratory: hematology, CA19-9, CEA, blood chemistry, and urinalysis.
- Obtain samples for PEGPH20 immunogenicity testing and send to the central laboratory.
- Administer piroxicam (20 mg) at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. Note: An analgesic non-steroidal agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

PEGPH20 Infusion

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

8.1.2.1.2.2. Cycle 2 and Beyond, Day 9

Before CIS and GEM Infusion

- Assess vital signs.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

CIS and GEM Infusion

- CIS IV infusion over 1 hour, 24 hours (±4 hours) after completion of PEGPH20 infusion.

- GEM IV infusion over 30 minutes, 24 hours (±4 hours) after completion of PEGPH20 infusion.

8.1.2.1.2.3. All Cycles Day 2

Before CIS and GEM Infusion

- Assess vital signs.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

CIS and GEM Infusion

- CIS IV infusion over 1 hour, 24 hours (±4 hours) after completion of PEGPH20 infusion.
- GEM IV infusion over 30 minutes, 24 hours (±4 hours) after completion of PEGPH20 infusion.

8.1.2.1.2.4. All Cycles Day 8

Before PEGPH20 Infusion

- Assess vital signs.
- Obtain samples for the following tests and send to the central laboratory: hematology and blood chemistry.
- Administer piroxicam (20 mg) at least 1 hour 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. Note: A non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

PEGPH20 Infusion

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

8.1.2.1.2.5. All Cycles Day 15

Before PEGPH20 Infusion

- Assess vital signs.
- Obtain hematology sample and send to the central laboratory.
- Administer piroxicam (20 mg) at least 1 hour 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, institutional practices, and

subject's convenience) to minimize the severity of MSEs. Note: A non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator.

- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

PEGPH20 Infusion

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

8.1.2.1.3. Selected Cycles from Cycle 3 Onwards, Day 15

- Obtain CT/MRI scans for tumor assessment (based on RECIST v1.1) at the end of Cycles 3 and then at the end of every third cycle thereafter (i.e., end of Week 3 of Cycles 6, 9, and beyond). Scans may be obtained any time on or after Day 15 (of Cycles 3, 6, 9, and every third 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. The tumor assessments scans obtained during the study should be archived in accordance with the standard local practice. The scans will be submitted to a CIV selected by the Sponsor for potential central review at a later timepoint. 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 is required for subjects with CR or PR to confirm response per RECIST v1.1 (details in Section 8.2.15).

8.1.2.2. Subjects Receiving PEGCISGEMATEZO Treatment (Run-in and Expansion)

8.1.2.2.1. Treatment Cycle 1

8.1.2.2.1.1. Cycle 1 Day 1

Before PEGPH20 and Atezolizumab Infusion

- Confirm subjects' eligibility based on inclusion and exclusion criteria.
- Perform physical examination.
- Perform the following assessments: vital signs, ECOG Performance Status, and weight/BSA.
- Obtain samples for the following tests and send to the central laboratory:
  - Hematology.
  - Blood chemistry. Note: Measurements of total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (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

AST and ALT values are within the ranges specified in the Inclusion Criterion. For total bilirubin, dosing can take place only if the total bilirubin is ≤3.0 × ULN.

- Urinalysis.
- Thyroid.

- Obtain samples for PEGPH20 and atezolizumab immunogenicity testing and send to the central laboratory.
- Obtain samples for CA19-9 and CEA testing and send to the central laboratory.
- Administer piroxicam (20 mg) at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. Note: A non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

PEGPH20 and Atezolizumab Infusion

- PEGPH20 IV infusion over 10 to 12 minutes (approximately 1 mL/min).
- Atezolizumab IV infusion over 60 minutes, 1 to 3 hours after completion of PEGPH20 infusion.

8.1.2.2.1.2. Cycle 1 Day 4 (Subjects Enrolled Under Protocol Amendment 3 Only)

Before PEGPH20 Infusion

- Assess vital signs.
- Administer piroxicam (20 mg) at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. Note: A non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

PEGPH20 Infusion

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

8.1.2.2.1.3. Cycle 1 Day 8

Before PEGPH20 Infusion

- Assess vital signs.
- Obtain samples for the following tests and send to the central laboratory:
  - Hematology
  - Blood chemistry. Note: Measurements of total bilirubin, 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 AST and ALT values are within the ranges specified in the Inclusion Criterion. For total bilirubin, dosing can take place only if the total bilirubin is ≤3.0 × ULN.
- Administer piroxicam (20 mg) at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. Note: A non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

PEGPH20 Infusion

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

8.1.2.2.1.4. Cycle 1 Day 9

Before CIS and GEM Infusion

- Assess vital signs.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole daily or OTC equivalent).
- Administer 1 mg/kg of enoxaparin .

CIS and GEM Infusion

- CIS IV infusion over 1 hour, 24 hours (±4 hours) after completion of PEGPH20 infusion.
- GEM IV infusion over 30 minutes, 24 hours (±4 hours) after completion of PEGPH20 infusion.

8.1.2.2.1.5. Cycle 1 Day 11 (Subjects Enrolled Under Protocol Amendment 3 Only)

Before PEGPH20 Infusion

- Assess vital signs.
- Administer piroxicam (20 mg) at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. Note: A nonsteroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg/day of enoxaparin.

PEGPH20 Infusion

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

8.1.2.2.1.6. Cycle 1 Day 15

Before PEGPH20 Infusion

- Assess vital signs.
- Obtain hematology sample and send to the central laboratory.
- Obtain blood chemistry sample and send to the central laboratory. Note: Measurements of total bilirubin, 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 AST and ALT values are within the ranges specified in the Inclusion Criterion. For total bilirubin, dosing can take place only if the total bilirubin is $\leq 3.0 \times$ ULN.
- Administer piroxicam (20 mg) at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. Note: A non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

PEGPH20 Infusion

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

8.1.2.2.1.7. Cycle 1 Day 18 (Subjects Enrolled Under Protocol Amendment 3 Only)

Before PEGPH20 Infusion

- Assess vital signs.
- Administer piroxicam (20 mg) at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. Note: A non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg/day of enoxaparin.

PEGPH20 Infusion

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

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

8.1.2.2.2.1. Cycle 2 and Beyond Day 1

Before PEGPH20 and Atezolizumab Infusion

- Perform urine/serum pregnancy test (WOCBP) at a local laboratory.
- Perform physical examination.
- Perform the following assessments: vital signs, ECOG Performance Status, and weight/BSA.
  - Obtain samples for the following tests and send to the central laboratory: hematology, urinalysis, CA19-9, CEA, and blood chemistry. Note that for Cycle 2 Day 1 only: Measurements of total bilirubin, 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 AST and ALT values are within the ranges specified in the Inclusion Criterion. For total bilirubin, dosing can take place only if the total bilirubin is $\leq 3.0 \times$ ULN. If a subject has any of the values outside the specified ranges for ALT, AST and total bilirubin on Day 1 of Cycle 2, the Investigator should discuss further dosing plans for the subject with the Sponsor.
- Obtain samples for PEGPH20 and atezolizumab immunogenicity testing and send to the central laboratory.
- Administer piroxicam (20 mg) at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. Note: A non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator.

- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

PEGPH20 and Atezolizumab Infusion

- PEGPH20 IV infusion over 10 to 12 minutes (approximately 1 mL/min).
- Atezolizumab IV infusion over 60 minutes, 1 to 3 hours after completion of PEGPH20 infusion. Atezolizumab may be administered over 30 minutes instead of 60 minutes if the first infusion in Cycle 1 is tolerated.

8.1.2.2.2.2. Cycle 2 and Beyond, Day 8

Before PEGPH20 Infusion

- Assess vital signs.
- Obtain samples for the following tests and send to the central laboratory: hematology, blood chemistry.
- Administer piroxicam (20 mg) at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. Note: A non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at discretion of the Investigator.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

PEGPH20 Infusion

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

8.1.2.2.2.3. Cycle 2 and Beyond, Day 9

Before CIS and GEM Infusion

- Assess vital signs.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole daily or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

CIS and GEM Infusion

- CIS IV infusion over 1 hour, 24 hours (±4 hours) after completion of PEGPH20 infusion.

- GEM IV infusion over 30 minutes, 24 hours (±4 hours) after completion of PEGPH20 infusion.

8.1.2.2.2.4. Cycle 2 and Beyond, Day 15

Before PEGPH20 Infusion

- Assess vital signs.
- Obtain hematology sample and send to the central laboratory.
- Obtain blood chemistry sample and send to the central laboratory.
- Administer piroxicam (20 mg) at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. Note: A non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

PEGPH20 Infusion

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

8.1.2.2.2.5. All Cycles Day 2

Before CIS and GEM Infusion

- Assess vital signs.
- Administer proton pump inhibitor (e.g., 20 mg omeprazole daily or OTC equivalent).
- Administer 1 mg/kg of enoxaparin.

CIS and GEM Infusion

- CIS IV infusion over 1 hour, 24 hours (±4 hours) after completion of PEGPH20 infusion.
- GEM IV infusion over 30 minutes, 24 hours (±4 hours) after completion of PEGPH20 infusion.

8.1.2.2.3. Selected Cycles from Cycle 3 Onwards, Day 1

- Obtain blood sample for testing of thyroid hormones (to be collected on Day 1 of Cycle 3 and every third cycle thereafter (i.e., Day 1 of Cycles 6, 9, etc.).

8.1.2.2.4. Selected Cycles from Cycle 3 Onwards, Day 15

- Obtain CT/MRI scans for tumor assessment (based on RECIST v1.1 and Immune-Modified RECIST) at the end of Cycles 3 and then at the end of every third cycle thereafter (i.e., end of Week 3 of Cycles 6, 9, and beyond). Scans may be

obtained any time on or after Day 15 (of Cycles 3, 6, 9, and every third 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. The tumor assessments scans obtained during the study should be archived in accordance with the standard local practice. The scans will be submitted to a CIV selected by the Sponsor for potential central review at a later timepoint. 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 is required to confirm disease progression based on Immune-Modified RECIST; and a confirmatory scan is required for subjects with CR or PR to confirm response per RECIST v1.1 (details in Section 8.2.15).

8.1.2.3. Subjects Receiving CISGEM (Expansion only)

8.1.2.3.1. Treatment Cycle 1

8.1.2.3.1.1. Cycle 1 Day 1

Before CIS and GEM Infusion

- Confirm subjects' eligibility based on inclusion and exclusion criteria.
- Perform physical examination.
- Perform the following assessments: vital signs, ECOG Performance Status and weight/BSA.
- Obtain samples for the following tests and send to the central laboratory: hematology, urinalysis, blood chemistry, CA19-9 and CEA.

CIS and GEM Infusion

- CIS IV infusion over 1 hour.
- GEM IV infusion over 30 minutes.

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

8.1.2.3.2.1. Cycle 2 and Beyond Day 1

Before CIS and GEM Infusion

- Perform urine/serum pregnancy test (WOCBP) at a local laboratory.
- Perform physical examination.
- Perform the following assessments: vital signs, ECOG Performance Status and weight/BSA.
- Obtain samples for the following tests and send to the central laboratory: hematology, blood chemistry, CA19-9, CEA, and urinalysis.

CIS and GEM Infusion

- CIS IV infusion over 1 hour.
- GEM IV infusion over 30 minutes.

8.1.2.3.2.2. All Cycles Day 8

Before CIS and GEM Infusion

- Assess vital signs.
- Obtain samples for the following tests and send to the central laboratory: hematology and blood chemistry.

CIS and GEM Infusion

- CIS IV infusion over 1 hour.
- GEM IV infusion over 30 minutes.

8.1.2.3.3. Selected Cycles from Cycle 3 Onwards, Day 15

- Obtain CT/MRI scans for tumor assessment (based on RECIST v1.1) at the end of Cycles 3 and then at the end of every third cycle thereafter (i.e., end of Week 3 of Cycles 6, 9, and beyond). Scans may be obtained any time on or after Day 15 (of Cycles 3, 6, 9, and every third 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. The tumor assessments scans obtained during the study should be archived in accordance with the standard local practice. The scans will be submitted to a CIV selected by the Sponsor for potential central review at a later timepoint. 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 is required for subjects with CR or PR to confirm response per RECIST v1.1 (details in Section 8.2.15).

8.1.2.4. End of Treatment Visit

The End of Treatment Visit procedures described below will be the same for all subjects, regardless of the study portion or the treatment, unless otherwise specified. 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 for other reasons. AEs and concomitant medications will be obtained and the following procedures should be performed:

- Perform the following assessments: physical examination, vital signs, measure weight/calculate BSA, 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, unless the latter was performed within the last 14 days.

- Administer proton pump inhibitor (e.g., 20 mg omeprazole daily or OTC equivalent) for subjects receiving PEGCISGEM and PEGCISGEMATEZO treatment.
- Obtain samples for the following tests and send to the central laboratory: hematology, blood chemistry, coagulation, and urinalysis.
- Obtain sample for PEGPH20 and atezolizumab immunogenicity testing (subjects receiving PEGCISGEM and PEGCISGEM ATEZO only) and testing of serum CA19-9 and CEA levels and send to the central laboratory.
- Obtain an End of Treatment tumor biopsy if deemed clinically feasible by the Investigator, at the time of disease progression per RECIST v1.1 (subjects receiving PEGCISGEM, PEGCISGEMATEZO, and CISGEM), loss of clinical benefit as determined by the Investigator (subjects receiving PEGCISGEM and PEGCISGEMATEZO), or unacceptable toxicity (subjects receiving PEGCISGEM, PEGCISGEMATEZO, and CISGEM).

8.1.2.5. 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 (or more frequently, if, required, prior to important study timepoints, including DMC meetings and database locks). 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 8.1.2.4). 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.

8.2.2. 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 (including bile duct adenocarcinoma 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 (allergy to bee stings, anaphylaxis, etc.) should also be captured on the Medical History eCRF page.

A complete medical history of bile duct adenocarcinoma (intrahepatic, extrahepatic, gallbladder) will be obtained at screening and 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. Body surface area (BSA) will be calculated from the height and weight.

8.2.8. ECOG Performance Status

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

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. Central Laboratory Tests

Hematology, blood chemistry, thyroid hormones, coagulation parameters, viral serology, and urinalysis will all be analyzed by the central laboratory. Central laboratory testing is mandatory

and must be performed; however, if central laboratory results cannot be obtained within the required timeframe, then local laboratory results may be used to for the purposes of eligibility determination at Screening and for measurement of liver function, including total bilirubin, 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). In such cases, results and reference ranges of the local laboratory will take precedence over those of the central laboratory (e.g., if a subject is eligible according to the local laboratory but ineligible according to the central laboratory, then that subject would still be considered qualified for study enrollment as per protocol). 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 atezolizumab US Prescribing Information (TECENTRIQ® US Prescribing Information 2018) advises monitoring of patients for changes in thyroid function at the start of treatment and periodically during treatment, the thyroid hormones free triiodothyronine (T3; or total T3 for sites where free T3 is not performed), 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).
- Viral serology: HIV, HBsAg, HBsAb, total HBcAb, HCV antibody; HBV DNA (for subjects with negative HBsAg result and positive total HBcAb result); HCV RNA (for subjects with positive HCV antibody result).
- 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 5 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).
- IUD.
- IUS.
- Bilateral tubal occlusion.
- Vasectomized partner.
- True sexual abstinence (defined as refraining from heterosexual intercourse if this is aligned with the preferred and usual lifestyle of the subject). Periodic abstinence, declaration of abstinence for the duration of the trial or withdrawal should not be considered as a highly effective method of contraception and therefore are not acceptable methods of contraception.

Participating men can be fertile or vasectomized. Fertile men are advised to use highly effective methods of contraception during the study and until 6 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.

A serum sample will also be collected from all subjects receiving PEGCISGEMATEZO and analyzed to determine if atezolizumab is eliciting a humoral immune response. Initial 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.

Refer to the current US Prescribing Information of atezolizumab for information related to immunogenicity of atezolizumab.

Refer to the current US Prescribing Information of CIS and GEM for information related to immunogenicity of CIS and GEM.

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 Bile Duct 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, including those obtained at Screening (baseline), will be evaluated locally for disease assessment using RECIST v1.1 and Immune-Modified RECIST.

For study eligibility, the Investigator must determine the presence of 1 or more tumors on CT/MRI scans performed within 28 days of Day 1. For subject eligibility in both portions of the study measurable disease must be determined using RECIST v1.1 (Appendix B). During the study, CT/MRI scans for objective tumor assessment (based on RECIST v1.1 and Immune-Modified RECIST) will be performed at the end of Cycle 3, and at the end of every third treatment cycle thereafter (i.e., end of Week 3 of Cycles 6, 9, and beyond). CT/MRI scans for RECIST v1.1 and Immune-Modified RECIST should be performed after the last dose in each cycle to allow time for reading of the scans by the local reviewer prior to start of subsequent cycles.

Per RECIST v1.1, a response of PR and CR should be confirmed by a repeat tumor imaging assessment no less than 28 days from the date the response was first documented. A confirmatory scan is required in both portions of the study for subjects with CR or PR for confirmation of response. This confirmatory scan may be performed at the earliest 28 days after the date of the first documented response (preferred) or at the next scheduled imaging timepoint, whichever is clinically indicated. Subjects who have a confirmatory scan need not undergo the next scheduled tumor imaging if the latter is less than 4 weeks after the confirmatory scan, unless clinically indicated. Subjects will return to regular scheduled imaging starting with the next scheduled imaging timepoint.

A confirmatory scan is required for subjects receiving PEGCISGEMATEZO treatment to confirm radiological disease progression, per Immune-Modified RECIST. This confirmatory scan should be obtained no sooner than 28 days after the initial scan that showed progression based on RECIST v1.1 (this can be the next scheduled tumor assessment scan).

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, unless the latter was performed within the last 14 days.

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.

8.2.15.1. Chest Computed Tomography to Exclude Pulmonary Embolism

The chest CT obtained during the screening period should be read locally to assess for the presence of PE. If a subject has signs and symptoms of PE after the initial screening scan was obtained, the scan should be repeated prior to enrollment (in Run-in)/randomization (in Expansion) (refer to Section 8.1.1).

8.2.16. Doppler Ultrasound Scanning for Assessment of Deep Vein Thrombosis

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

8.2.17. Pharmacokinetic Assessments

Plasma samples will be collected to assess the potential effects of atezolizumab, CIS and GEM on the PK of PEGPH20 (as specified in Table 4 and Table 5). Additionally, plasma samples will also be collected to assess the PK of CIS and GEM. Serum samples will be collected to assess the PK of atezolizumab. Post-dose PK timepoints will be specified relative to PEGPH20, atezolizumab, CIS, and GEM infusions. 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 therapy with any of the other study drugs, at the discretion of the Investigator, PK samples of those drugs must be collected.

8.2.18. CA19-9

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

8.2.19. CEA

The CEA test is a blood test from the tumor marker category. Serum samples will be collected from all subjects to assess the effect of treatment on CEA levels and sent to the central laboratory for analysis.

8.2.20. Pharmacodynamic and Biomarker Assessments

This study will collect samples for pharmacodynamic and biomarker assessments in all subjects (where not prohibited by local regulations). Sample types collected include tumor, blood, and plasma samples. Any sample or derivatives (such as DNA, 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.

8.2.20.1. Tumor Biopsies

Tumor tissue needs to meet specific tissue sample requirements (see Laboratory Manual).

Tumor tissue will be sent to a central laboratory and tested for HA levels retrospectively using an exploratory investigational diagnostic assay. This assay uses an affinity-histochemistry-based staining method to evaluate HA levels in tumor biopsies. PD-L1 expression levels will also be tested in the tumor tissue retrospectively. Exploratory biomarkers may also be assessed.

If deemed clinically feasible by the Investigator, an End of Treatment biopsy will be collected at the time of disease progression per RECIST v1.1, loss of clinical benefit as determined by the Investigator, or unacceptable toxicity, in subjects receiving PEGCISGEM and PEGCISGEMATEZO. In the CISGEM control arm, tumor tissue will be collected at the time of disease progression per RECIST v1.1 or unacceptable toxicity. The samples 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 chemotherapy effects and to potentially identify resistance mechanisms.

8.2.20.2. Blood Samples

Blood samples will be collected according to timepoints listed in Table 4 and Table 5.

8.2.20.2.1. Plasma Samples

Plasma HA is a pharmacodynamic marker 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 will be analyzed for exploratory biomarkers (such as protein, circulating tumor DNA) to assess their potential prognostic or predictive value.

8.2.20.2.2. Pharmacogenetic Samples

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

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

8.3. Study Drug Administration

Each treatment cycle is 21 days (3 weeks).

PEGPH20, CIS, GEM, and atezolizumab will be administered as specified in the Schedule of Events Table 2 and Table 3.

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

This section provides guidance for dose interruptions and modifications of study treatment. Dose modifications for chemotherapy are permitted in the Run-in and Expansion portions of the study. Dose interruptions are allowed for atezolizumab in both the Run-in and Expansion portions of the study. PEGPH20 dose interruption and dose reduction is allowed in both the Run-in and Expansion portions of the study. No dose modifications of atezolizumab are allowed in this study. Dose modification guidelines are provided in Section 8.3 for PEGPH20, CIS and GEM. Guidance for atezolizumab dose interruption and discontinuation due to AEs are provided in the atezolizumab Investigator's Brochure. Dose reduction levels of PEGPH20 are provided in Table 10 of Section 8.3.1.3 . Additional dose modification guidelines for CIS and GEM are provided in the Prescribing Information of these chemotherapeutic agents.

Missed or Held Doses of Study Drugs

Subjects receiving PEGCISGEM:

Cycle 1 does not begin until PEGPH20 is administered.

If PEGPH20 is permanently discontinued, the dosing of CIS and GEM should continue per study protocol schedule.

If both CIS and GEM are anticipated to be missed or held on Day 2 of Cycle 2+, PEGPH20 must also be held until chemotherapy can be restarted.

If both CIS and GEM are anticipated to be missed or held on Day 9, dosing with PEGPH20 should continue per protocol schedule.

If CIS is missed, held, or permanently discontinued, dosing with GEM and PEGPH20 should continue per protocol schedule. If GEM is anticipated to be missed, held, or permanently discontinued, CIS should not be administered.

If both GEM and CIS are permanently discontinued, PEGH20 must also be permanently discontinued.

Subjects receiving PEGCISGEMATEZO:

Cycle 1 does not begin until PEGPH20 is administered.

If PEGPH20 is permanently discontinued, the dosing of CIS, GEM, and atezolizumab should continue per protocol schedule.

If both CIS and GEM are anticipated to be missed or held on Day 2 of Cycle 2+, PEGPH20 and atezolizumab should also be held until chemotherapy can be restarted.

If both CIS and GEM are anticipated to be missed or held for Day 9, dosing with PEGPH20 should continue per protocol schedule.

If CIS is missed, held, or permanently discontinued, dosing with GEM, PEGPH20, and atezolizumab should continue per protocol schedule. If GEM is anticipated to be missed, held, or permanently discontinued CIS should not be administered.

If both GEM and CIS are permanently discontinued, PEGH20 and atezolizumab dosing should continue per protocol schedule.

If atezolizumab, GEM, and CIS are permanently discontinued then PEGPH20 (all study treatment) must also be permanently discontinued.

If GEM, CIS, and PEGPH20 are permanently discontinued, atezolizumab dosing should continue per protocol schedule.

Subjects receiving CISGEM (Control):

If CIS is missed, held, or permanently discontinued, dosing with GEM should continue per protocol. If GEM is missed, held, or permanently discontinued CIS should not be administered.

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 and as per institutional guidelines. 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 Reactions

In the event of a hypersensitivity reaction, the PEGPH20 and atezolizumab infusion should be managed per Table 8 below and the symptoms should be treated as necessary. Blood should be drawn and analyzed per the Sponsor's instructions to confirm the reaction (e.g., PEGPH20-specific immunoglobulin E and serum tryptase levels). Halozyme should be contacted immediately (see study manual for contact information) so that current knowledge of laboratory testing can be provided to the site.

Table 8: Guidelines for Management of PEGPH20 or atezolizumab infusion-related reactions

Event	Action to Be Taken
IRR and anaphylaxis	• For anaphylaxis precautions, refer to Appendix E.
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the Investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, administer oral premedication with antihistamine and anti-pyretic and monitor closely for IRRs.
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue treatment and contact Medical Monitor.[a]

Abbreviations: IRR = infusion-related reaction; IV = intravenous

[a] Resumption of treatment may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

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 9 for guidelines.

Table 9: 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 exception of high-dose 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 exception of high-dose 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 exception of high-dose 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 exception of high-dose 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[a]), 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 9: 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 (refer to Table 10 below). • 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)	
Grade 1 visceral/splanchnic vein thrombosis (associated with underlying disease of CCA and gallbladder adenocarcinoma)	No change.
Any Grade TE event (except superficial vein thrombosis; Grade 1 visceral/splanchnic vein thrombosis [associated with underlying disease of CCA and gallbladder adenocarcinoma])	• Discontinue PEGPH20 treatment permanently and treat event per current NCCN guidelines until documented resolution of event. Treatment with the other drugs may continue as deemed appropriate by the Investigator.

Abbreviations: CCA = cholangiocarcinoma; MSE = musculoskeletal event; NCCN = National Comprehensive Cancer Network; OTC = over-the-counter; PEGPH20 = PEGylated recombinant human hyaluronidase; TE = thromboembolic.

[a]Since this study uses an immunotherapeutic agent and steroids may suppress an immune response, steroids may be used at the Investigator's discretion to treat ≥ Grade 3 MSEs that are refractory to non-steroid management only.

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 for management of TE events, refer to Section 10.1.1.

Table 10: PEGPH20 Dose Reduction Guidelines

Starting PEGPH20 Dose	First Allowed Dose Reduction	Second Allowed Dose Reduction	Third Allowed Dose Reduction
3.0 µg/kg	2.2 µg/kg	1.6 µg/kg	Discontinue PEGPH20 treatment
2.2 µg/kg	1.6 µg/kg	Discontinue PEGPH20 treatment	-
1.6 µg/kg	Discontinue PEGPH20 treatment	-	-

The lowest dose level for dose reduction will be 1.6 µg/kg of PEGPH20. Re-escalations of PEGPH20 are allowed in both portions of the study at the Investigator's discretion with written permission by a Halozyme medical monitor.

8.3.2. Atezolizumab

8.3.2.1. Atezolizumab Administration

Atezolizumab will be administered per the US Prescribing Information (as an IV infusion at a fixed dose of 1200 mg over 60 minutes on Day 1 of each 21-day cycle, 1 to 3 hours after PEGPH20. Note that in Cycle 2 and beyond, atezolizumab may be administered as an IV infusion over 30 minutes instead of 60 minutes if the first infusion in Cycle 1 is tolerated (TECENTRIQ® US Prescribing Information 2018).

All Cycle Day 1 administrations of atezolizumab should occur 1 to 3 hours after PEGPH20 administration.

8.3.2.2. Identified Risks of Atezolizumab Treatment

Refer to the current Atezolizumab US Prescribing Information for the identified risks associated with atezolizumab treatment.

8.3.2.3. Atezolizumab Dose Adjustment and Toxicity Management

Dose adjustments (interruption, and discontinuation) and toxicity management should be undertaken per the current US Atezolizumab Prescribing Information, Appendix F, and the current Atezolizumab Investigator's Brochure.

8.3.3. Cisplatin and Gemcitabine

Premedication with antiemetics will be administered as standard-of-care prior to CIS and GEM infusions. The use of steroids during treatment in the study should be avoided unless emesis is not controlled with other antiemetics.

8.3.3.1. Cisplatin Administration

CIS will be administered as an IV infusion at 25 mg/m^2 over 1 hour with prior hydration and electrolyte supplementation with potassium and magnesium per individual institutional standard on Day 2 and Day 9 of each 21-day cycle to subjects receiving PEGCISGEM and

PEGCISGEMATEZO. In the Control arm, CIS will be administered as an IV infusion at 25 mg/m^2 over 1 hour with prior hydration and electrolyte supplementation with potassium and magnesium per individual institutional standard on Day 1 and Day 8 of each 21-day cycle.

Please refer to the current package insert for the description and composition of this drug.

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

8.3.3.2. Gemcitabine Administration

After completion of the CIS infusion, GEM will be administered as an IV infusion at 1000 mg/m^2 over 30 minutes per institutional standard on Day 2 and Day 9 of each 21-day cycle to subjects treated with PEGCISGEM and PEGCISGEMATEZO. In the Control arm, GEM will be administered as an IV infusion at 1000 mg/m^2 over 30 minutes per institutional standard on Day 1 and Day 8 of each 21-day cycle.

Please refer to the current Prescribing Information for the description and composition of this drug.

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

8.3.3.3. Identified Risks of CIS and GEM Treatment

Refer to the current CIS package insert and GEM Prescribing Information for the identified risks associated with CIS and GEM treatments.

8.3.3.4. Cisplatin and Gemcitabine Dose Adjustment and Toxicity Management

CIS and GEM regimen is usually well tolerated and most dose modifications will be due to hematological toxicity and assessment of renal function.

Hematological toxicity

GEM will be dose-reduced if hematological toxicity occurs. CIS can be dose-reduced for cases of hematological toxicity if it is standard practice for the site. The dose to be administered will depend on the complete blood count (CBC) result on the day of treatment.

WBC (x109/L)	And /or	ANC (x109/L)	And/ or	Platelets (x1000/mm^3)	Gemcitabine Dose	Cisplatin Dose
≥2		≥1		≥100	Full	Full
1-1.9		0.5-0.9		50-99	75% dose	Full**
<1		<0.5		<50	Delay*	Delay

* If delay is >3 weeks for hematological toxicity, the patient will be withdrawn from treatment.
Abbreviations: ANC = absolute neutrophil count; WBC = white blood cell.
** CIS can be reduced to 75% of the standard dose for cases of hematological toxicity, if it is standard practice for the site.

Note: the dose of CIS and GEM will be re-escalated to full dose upon recovery of hematological toxicity in order to maintain the dose intensity of therapy.

Renal toxicity

CIS dosage will depend on renal function, (Cockcroft Gault formula):

	Cisplatin	Gemcitabine
Estimated GFR ≥45 mL/min	Full dose	Full dose
Estimated GFR <45 mL/min*	Omit	Full dose

Abbreviations: GFR = Glomerular Filtration Rate
*Repeat the creatinine clearance assessment (consider using the more accurate isotope GFR method, if not available 24 hour urine creatinine clearance could be used) ensuring the patient is adequately hydrated prior to this test and further cisplatin administration. Proceed with cisplatin if the repeated reading is ≥45ml/min, otherwise cisplatin is to be omitted until recovery of renal function. If cisplatin has to be omitted, continue with gemcitabine dosing according to CBC. If a sudden increase in creatinine occurs, hemolytic uraemic syndrome should be ruled out.

Other toxicity

No dose reduction/modification is required for:

Alopecia (any grade)	
Lethargy (grade 1-2)	
Nausea/vomiting (grade 1-2)	May have been reduced from grade 3-4 by appropriate use of antiemetics
Edema (grade 1-2)	Give postural advice, consider appropriate diuretics

Consider dose-modifications* for:

Lethargy (grade 3-4)	Reduce gemcitabine by 25%
Nausea/vomiting (grade 3-4)	Ensure optimal use of antiemetics (according to local policy). Delay until recovery to baseline, then: Omit cisplatin first. If no improvement reduce gemcitabine by 25%.
Peripheral neuropathy (grade 1-2)	Delay cisplatin until recovery to baseline, then continue at full dose. If no recovery, treat as for grade 3-4. Continue with gemcitabine (full dose).
Peripheral neuropathy (grade 3-4)	Omit cisplatin from further treatment. Continue with gemcitabine (full dose).
Edema (grade 3-4)	Dipstick urine test for protein followed by full 24-hour urinary protein estimation if result ≥+ Delay until recovery to baseline (with use of appropriate diuretics). Then reduce gemcitabine by 25%.
Tinnitus	No dose modification required if full recovery between cycles. Omit cisplatin if no recovery between cycles. Continue gemcitabine (full dose).

Stop allocated treatment for:

Lethargy (grade 3-4)**	Which has not responded to dose modification
Nausea/vomiting (grade 3-4)**	Which has not responded to optimal antiemetics or dose reduction
Edema (grade 3-4)	Which has not responded to dose modification and use of appropriate diuretics
Pulmonary toxicity (grade 2-4)	Supportive therapy (high dose steroids) should be initiated immediately

* Clinician discretion as to whether a particular non-hematological toxicity requires a dose reduction or treatment delay

** If delay is >3 weeks for non-hematological toxicity (excluding biliary tract obstruction)

Biliary tract obstruction during treatment

In the event of the development of obstructive jaundice due to biliary tract obstruction, appropriate measures will be undertaken to diagnose (e.g., by ultrasound and/or CT scan) and relieve the obstruction (e.g., by endoscopic retrograde cholangiopancreatography/ percutaneous transhepatic cholangiography +/- stent insertion/drainage). All study treatments will be deferred until the Liver Function Tests have improved to the pre-treatment eligibility levels (i.e., total bilirubin ≤1.5 × ULN; ALT, AST, and alkaline phosphatase ≤2.5 × ULN). All study treatments may then resume at the start of the next treatment cycle.

8.4. Excluded Concomitant Medications and Study Restrictions

Concurrent chronic use of IV heparin is prohibited; however, for acute TE events, IV heparin may be used. PEGPH20 administration must be stopped during this period. Use of megestrol acetate and any megestrol acetate-containing drugs 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.

The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the efficacy of atezolizumab. However, systemic corticosteroids are recommended, at the discretion of the Investigator, for the treatment of specific AEs when associated with atezolizumab therapy (refer to the current US Prescribing Information for details). With the exception of inhaled, intranasal or intra-articular steroids, and low-dose steroids administered to treat AEs, PEGPH20 and atezolizumab administration must be held when any other systemic steroids are administered for management of an AE and may be restarted when the steroids have been discontinued.

Live attenuated vaccines should not be administered throughout the study period and for 5 months after the last dose of atezolizumab.

Systemic immunostimulatory agents are also prohibited during the treatment period.

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.

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 30 kDa PEG and rHuPH20.

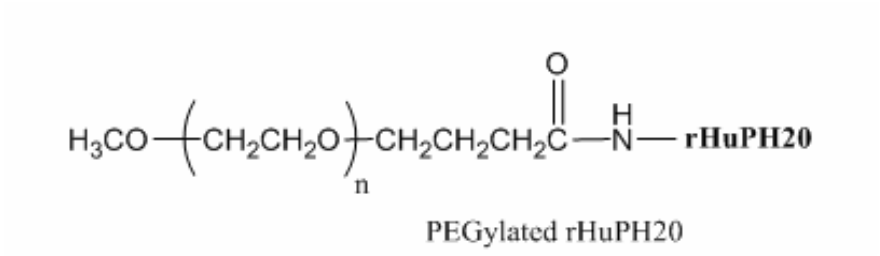
Chemical Name

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 PEGPH20 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 average molecular weight is approximately 220,000 Da (range of approximately 90,000 to 320,000 Da).

9.1.2. Atezolizumab

Atezolizumab is a PD-L1 antibody indicated for the treatment of patients with:

- Locally advanced or metastatic urothelial carcinoma who:
  - Are not eligible for cisplatin-containing chemotherapy, or
  - Have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for the indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

- Metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on Food and Drug Administration (FDA) approved therapy for these aberrations prior to receiving atezolizumab.

Atezolizumab will be considered investigational for the purpose of this study since the combination of atezolizumab with PEGPH20, CIS and GEM has not been indicated as yet for the treatment of the populations studied in this trial.

Refer to the current Atezolizumab Prescribing Information for a thorough description and diagram of the structure of atezolizumab.

9.1.3. Cisplatin

CIS is a cytotoxic chemotherapeutic drug that triggers apoptosis or programmed cell death by binding to and causing crosslinking of DNA. It is indicated as therapy to be employed for the following:

- Metastatic Testicular Tumors - In established combination therapy with other approved chemotherapeutic agents in patients with metastatic testicular tumors who have already received appropriate surgical and/or radiotherapeutic procedures.
- Metastatic Ovarian Tumors - In established combination therapy with other approved chemotherapeutic agents in patients with metastatic ovarian tumors who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination consists of CIS and cyclophosphamide. CIS as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumors refractory to standard chemotherapy who have not previously received CIS therapy.
- Advanced Bladder Cancer - CIS is indicated as a single agent for patients with transitional cell bladder cancer which is no longer amenable to local treatments, such as surgery and/or radiotherapy.

Although CIS is not indicated for the treatment of biliary tract cancers it is considered the non-label standard-of-care therapy for biliary tract cancers in combination with GEM.

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

9.1.4. Gemcitabine

GEM is a nucleoside metabolic inhibitor indicated:

- In combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.
- In combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.
- In combination with cisplatin for the treatment of NSCLC.
- As a single agent for the treatment of pancreatic cancer.

Although GEM is not indicated for the treatment of biliary tract cancers it is considered the non-label standard-of-care therapy for biliary tract cancers in combination with CIS.

Refer to the current GEM Prescribing Information for a thorough description and diagram of GEM.

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 300 mcg/mL PEGPH20 with 10 mM succinic acid, 130 mM NaCl, and 10 mM L-methionine at a pH of 6.2. Each vial contains 1.0 mL (0.30 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 light blue plastic flip-off cap. This drug product is provided as a refrigerated formulation and should be stored at 2°C to 8°C before use. Label information is provided in the Pharmacy Manual.

9.2.2. Atezolizumab

Atezolizumab injection is a sterile, preservative-free, and colorless to slightly yellow solution for IV infusion supplied as a carton containing one 1200 mg/20 mL single-dose vial.

Label information is provided in the Pharmacy Manual.

9.2.3. Cisplatin

CIS lyophilized powder or concentrate for solution for infusion may be utilized.

Cisplatin Lyophilized Powder

CIS for injection, USP is a white to light yellow lyophilized powder. Each amber vial of Plantinol® contains 50 mg CIS, 450 mg sodium chloride, USP, and 500 mg mannitol, USP.

Label information is provided in the Pharmacy Manual.

Cisplatin Concentrate Solution for Injection

CIS Injection is a clear, light-yellow, sterile aqueous solution available in amber vials containing 1 mg/mL of CIS. One mL of infusion concentrate 1 mg/mL contains: 1 mg CIS (USP), 9 mg sodium chloride, hydrochloric acid and/or sodium hydroxide to pH of 3.2 to 4.4, and water for injection. CIS Injection, 1 mg/mL, is supplied in multiple dose vials containing 50 mL and 100 mL.

Label information is provided in the Pharmacy Manual.

9.2.4. Gemcitabine

GEM lyophilized powder or concentrate for solution for infusion may be utilized.

Gemcitabine Lyophilized Powder

GEM is a white to off-white lyophilized powder for reconstitution with 0.9% sodium chloride injection without preservatives. GEM is supplied in sterile single-use vials as follows: 1 g white to off-white, lyophilized powder in 50 mL vials.

Label information is provided in the Pharmacy Manual.

Gemcitabine Concentrate for Solution for Injection

GEM is a sterile concentrate for solution for infusion that must be diluted before use. This is a sterile, clear, colorless or light straw-colored solution, practically free from visible particles.

Presentation: 1 g/26.3 mL. Strength: 38 mg/mL, Quantity of GEM: 1g. Volume of Solution: 26.3 mL.

Label information is provided in the Pharmacy Manual.

9.3. Study Drug Storage

9.3.1. PEGPH20

PEGPH20 drug product, supplied at a concentration of 0.30 mg/mL, is a liquid formulation and should be stored at 2°C to 8°C before use. Stability testing of this PEGPH20 drug product was initiated following general International Conference on Harmonisation (ICH) guidelines at 5°C ±3°C, and concurrent stability evaluation is ongoing. The Sponsor will monitor drug stability and provide updates on an ongoing basis.

9.3.2. Atezolizumab

Atezolizumab should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. It should not be frozen or shaken.

Atezolizumab does not contain a preservative and should be administered immediately once prepared.

If diluted atezolizumab infusion solution is not used immediately, it can be stored either:

- At room temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration for infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours.

9.3.3. Cisplatin

Cisplatin Lyophilized Powder

Unopened vials of dry powder are stable for the lot life indicated on the package when stored at room temperature (25°C, 77°F). The reconstituted solution is stable for 20 hours at room temperature (25°C, 77°F). Solution removed from the amber vial should be protected from light if it is not to be used within six hours.

Important Note: Once reconstituted, the solution should be kept at room temperature (25°C, 77°F). If the reconstituted solution is refrigerated a precipitate will form.

Cisplatin Concentrate Solution for Injection

CIS concentrate solution for injection should be stored at 20°C to 25°C (68°F to 77°F) [refer to USP Controlled Room Temperature] and not refrigerated. The unopened container must be protected from light.

9.3.4. Gemcitabine

Gemcitabine Lyophilized Powder

Unopened vials of GEM lyophilized powder are stable until the expiration date indicated on the package insert when stored at controlled room temperature 20°C to 25°C (68°F to 77°F), however, as also noted in the package insert, there is allowance for excursions between 15°C and 30°C (59°F and 86°F) [refer to USP Controlled Room Temperature].

GEM lyophilized powder must be retained in the original package to protect from bright light.

Refer to the package insert for storage conditions after preparation.

Gemcitabine Concentrate for Solution for Injection

Unopened vials of GEM Concentrate for Solution are stable until the expiration date indicated on the package when stored at 2°C to 8°C (36°F to 46°F). GEM Concentrate for Solution must not be frozen.

Refer to the package insert for storage conditions after preparation.

9.4. Study Drug Preparation

9.4.1. PEGPH20

Instructions for preparing PEGPH20 can be found in the Pharmacy Manual.

9.4.2. Atezolizumab

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

9.4.3. Cisplatin

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

9.4.4. Gemcitabine

GEM 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 the Sponsor, or as per Institution policy. The study drugs are 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 drugs 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; dose modifications (e.g., interruptions and delays); medical history; concomitant medications; immunogenicity (PEGPH20 and atezolizumab ADA), hematology, blood chemistry, 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 ICC, ECC, and gallbladder adenocarcinoma.

Subjects will be screened for TE events during the screening visit. Doppler ultrasound of both legs (Section 8.2.16) and chest CT (Section 8.2.15.1) will be performed during screening to exclude subjects with DVT and PE.

If a DVT or PE is detected before study treatment begins on Cycle 1 Day 1, the subject will be taken off study and will enter long-term follow-up. If a DVT or PE is detected during treatment, PEPGH20 will be held. Subjects should be treated with therapeutic doses of low molecular weight heparin and continue with chemotherapy and immunotherapy (if applicable) and be monitored per standard practice (i.e., routine Doppler ultrasound or chest CT scans and other routine laboratory testing).

To minimize the occurrence of TE events, prophylaxis for TE events will be given. Prophylactic enoxaparin will be administered at 1 mg/kg/day to all subjects receiving PEGPH20 (see Section 10.1.1 for additional details). If enoxaparin is discontinued for any reason, PEGPH20 will also be discontinued. Treatment with other drugs, however, may continue as deemed appropriate by the Investigator.

TE events should be managed per institutional guideline. PEGPH20 must be permanently discontinued for any TE event (with the exception of superficial venous thrombosis and Grade 1 visceral/splanchnic vein thrombosis [associated with underlying disease of CCA and gallbladder adenocarcinoma]).

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

10.1.1. Enoxaparin Management

All subjects receiving PEGPH20, including subjects in the PEGCISGEM and PEGCISGEMATEZO arms enrolled through Protocol Amendment 2 and the additional cohort of subjects enrolled under Protocol Amendment 3 receiving PEGCISGEMATEZO, will be administered prophylactic enoxaparin subcutaneously at a dose of 1 mg/kg/day. This is the same dosage administered to subjects with metastatic PDA in completed Phase 2 Study HALO-109-202 and ongoing Phase 3 Study HALO-109-301 of PEGPH20 in combination with GEM and NAB.

The change in enoxaparin dosage from a fixed dose of 40 mg/day to a weight-adjusted dose in subjects receiving PEGPH20 in the current study follows an ongoing review of safety data which, to date, identified in the PEGCISGEMATEZO arm a total of 5 TE events (16.7% of subjects dosed) vs. no TE events in the PEGCISGEM arm and 1 TE event (10% of subjects dosed) in the CISGEM arm, as communicated in a letter to Investigators dated 22 March 2019. The reported incidence of venous TE events in patients with biliary tract cancer is 11.5% (Larsen 2015). In Stage 2 of Study HALO-109-202, prophylaxis with enoxaparin 40 mg/day reduced the incidence of TE events in the PAG arm from 43% in Stage 1 (no enoxaparin prophylaxis) to 28%. A subsequent increase in the enoxaparin dose to 1 mg/kg/day in Stage 2 reduced the incidence further to 10% (Halozyme Clinical Study Report HALO-109-202 and Section 4.4.7.2).

Enoxaparin will be administered prior to the infusion of PEGPH20.

The dosage of enoxaparin of 1 mg/kg/day will be based on the subject's screening weight and should be modified if the subject's weight changes by 10%, or per institution's policy. Institution's rounding practices may be used when calculating the dose of enoxaparin. Efforts should be made to administer the calculated 1 mg/kg dose (± 10%); however, if prefilled syringes are used, rounding may be performed. If the difference between the rounded dose and the expected dose based on weight is greater than 20%, the Sponsor should be consulted. Refer to Table 11 for examples of rounding based on the expected enoxaparin dose.

Table 11: Enoxaparin 1 mg/kg/day Dosage

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

Enoxaparin dosing should be held or reduced per standard institutional guidelines for thrombocytopenia. Enoxaparin dosing for an acute TE event on study should also be managed per institutional guidelines.

In situations when enoxaparin is held, administration of PEGPH20 should be stopped during the holding period. All other study treatments may continue according to the dose modification sections for the respective therapy (See Section 8.3.3.4).

Enoxaparin treatment should be managed per institutional guidelines when the subject is permanently removed from PEGPH20 treatment.

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 or until initiation of new systemic anti-cancer therapy, whichever occurs first, and SAEs and AEs of special interest will continue to be reported until 90 days after the last dose of study drug or until initiation of new systemic anti-cancer therapy, whichever occurs first. AEs related to disease progression should not be collected or recorded, unless the Investigator considers the AE to be at least possibly related to study medication. 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 except for disease progression (see Section 10.4.3 for details) 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 into the study specific SAE form and send any other available pertinent information (e.g., hospital records, laboratory results) 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, entry of the new information into the electronic data capture (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 (Version 4.03 [14 June 2010]) should be utilized when grading TE events. Table 12 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 (Version 4.03 [14 June 2010]) should be used.

Table 12: 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 12: 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. Adverse Events of Special Interest for Atezolizumab (Immediately Reportable to the Sponsor)

AEs of special interest are required to be reported by the Investigator 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).

AEs of special interest for atezolizumab include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law, based on the following criteria:
  - Treatment-emergent ALT or AST >3 × baseline value in combination with total bilirubin >2 × ULN, of which ≥35% is direct bilirubin
  - Treatment-emergent ALT or AST >3 × baseline value in combination with clinical jaundice

- Suspected transmission of an infectious agent by the study treatment, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Vasculitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT >10 × ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

10.4.3. Disease-Related Events That Are Endpoints

For the purposes of this study in subjects with ICC, ECC, and gallbladder 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 by treatment. 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 qualifies as an SAE.

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 Institutional Review Board (IRB)/Ethics Committee (EC) reporting requirements.

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

Halozyme will conduct reviews of all available AEs at the end of the PEGCISGEM and PEGCISGEMATEZO Run-in portions and at a minimum of once every 12 weeks during 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 9).

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 atezolizumab or CIS or GEM. The Investigator should make this decision after careful consideration of the following questions:

- Does the AE follow a reasonable temporal sequence from administration of study drug?
- Can the AE be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapy?
- Do the AE symptoms disappear or decrease on cessation of study drug or reduction in study drug dose? (There are exceptions when an AE does not disappear on discontinuation of the drug, yet drug relatedness clearly exists [e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia])
- 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 current Prescribing Information for atezolizumab, CIS, and/or GEM for the summary of risks in this specific population. Based on its mechanism of action, atezolizumab, CIS and GEM can cause fetal harm when administered to a pregnant woman. WOCBP should therefore use highly effective contraception during treatment with the study drugs and refrain from breast feeding for 5 months after the last dose of the last study drug is administered in in all subjects receiving their same treatment. Pregnancy within 150 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 of the pregnancy). Follow-up should occur monthly and should be documented in the study file. A follow-up Pregnancy Report Form must be completed for each follow-up contact with the subject or 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, atezolizumab, CIS, and GEM will be administered by IV infusion at a qualified and experienced clinical study site. The potential for drug overdose is therefore minimal. However, should an overdose occur, the infusion should be stopped immediately. A blood PK plasma sample should be taken as soon as possible, with a notation of the time of sampling relative to the time of 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 atezolizumab, CIS, and GEM should be managed per the current respective 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

A DMC will periodically review safety data in the Run-in and Expansion portions of the study 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 CIS or GEM or atezolizumab), 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 last dose of study drug on the Concomitant Medications eCRF. Only those concomitant medications administered for ongoing AEs during the 30 days post the last dose of study drug are required to be recorded in the Adverse Event eCRF. Anti-cancer medications administered within 30 days post the last dose of study drug will be captured separately and should not be recorded as concomitant medications on the concomitant medication 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, OTC drugs and physical therapy can also be used at the Investigator's discretion and should be documented and recorded in the eCRF.

Since this study uses an immunotherapeutic agent (atezolizumab) and dexamethasone and other steroids may suppress an immune response, steroids can only be used in some exceptional circumstances as detailed in Section 10.12.3.

Steroid usage must be documented and recorded in the eCRF.

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

Antiemetics administered prior to CIS and GEM infusions should be documented and recorded in the eCRF.

10.12.1. Piroxicam and Toradol

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

Piroxicam (20 mg) will be administered at least 1 hour 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, institutional practices, and subject's convenience) to minimize the severity of MSEs. Note that a non-steroidal analgesic agent (at a dose equivalent to 20 mg of piroxicam) may be administered instead of piroxicam to reduce potential MSEs, at the discretion of the Investigator. 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 side effects are observed following administration of NSAIDs, the dosing of piroxicam may be adjusted at the Investigator's discretion. The Investigator may also choose alternative analgesic agents if NSAIDs are not tolerated.

10.12.2. Enoxaparin

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

All subjects receiving PEGPH20 will be given enoxaparin 1 mg/kg/day for prophylaxis of TE events (details in Section 10.1.1).

If enoxaparin is discontinued for any reason, PEGPH20 will also be discontinued. Treatment with the other drugs, however, may continue as deemed appropriate by the Investigator.

10.12.3. Steroids

Since this study uses an immunotherapeutic agent (atezolizumab) and dexamethasone and other steroids may suppress an immune response, steroids should only be used in the following exceptional circumstances:

- When prescribed by the Investigator to treat ≥ Grade 3 MSEs that are refractory to non-steroid management (refer to Section 8.3.1.3, Table 9 for further details)
- For management of specific AEs as listed in Section 8.3.1.2, Section 8.3.3.4 and/or the current atezolizumab US Prescribing Information and Investigator's Brochure
- To treat emesis or other AEs that are not controlled with non-steroidal medications
- Low-dose steroids may be administered at the discretion of the Investigator to treat other AEs.

The following steroids are allowed (see also Section 7.2):

- Inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for subjects with orthostatic hypotension, chronic obstructive pulmonary disease, or adrenocortical insufficiency
- Thyroid-replacement hormone
- Low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, fluocinolone 0.01%, desonide 0.05%, alclometasone dipropionate 0.05%) for subjects with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., subjects with psoriatic arthritis)

With the exception of the allowed steroids listed above and low-dose steroids to treat AEs, PEGPH20 and atezolizumab administration must be held if steroids are administered to treat AEs and can only be restarted once the steroid is discontinued.

10.12.4. Hydration and Electrolyte Supplementation

Hydration and electrolyte supplementation with potassium and magnesium must be given prior to CIS infusion per individual institutional standards.

10.12.5. Antiemetics

Premedication with antiemetics will be administered as standard-of-care to all subjects prior to chemotherapy (CIS and GEM infusions). The use of steroids during treatment in the study will be avoided unless emesis is not controlled with other antiemetics.

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. Data collected during the Run-in portion will be summarized by PEGPH20 dose levels tested with each combination. Results in the Expansion portion will be summarized for the 3 treatment arms randomized as well as the 3 treatments arms combined (total). Data from the non-randomized PEGCISGEMATEZO cohort enrolled under Protocol Amendment 3 will be summarized separately. 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, randomized study.

11.1.2. Sample Size

This study is planned to enroll approximately 77 to 85 subjects.

In the Run-in portion approximately 6 subjects will receive PEGPH20 plus CIS plus GEM, then a cohort of 6 subjects will receive PEGPH20, atezolizumab, CIS, and GEM when the PEGCISGEM cohort clears the safety evaluation. Additional dosing cohorts may be evaluated in the Run-in portion if the initial dose of PEGPH20 utilized in the combinations tested is deemed unsafe and/or intolerable. An additional 8 subjects may be enrolled in the Run-in portion to further assess the tolerability of PEGPH20 in order to establish an acceptable safety profile prior to randomization in the Expansion Portion of the study.

In the Expansion portion, approximately 50 subjects will be enrolled and randomized in a 2:2:1 ratio into PEGCISGEMATEZO, PEGCISGEM, and CISGEM treatment arms, stratified by geographical region (North America and Asia) and cancer type (CCA and gallbladder).

For the approximately 50 subjects enrolled in the Expansion portion through Protocol Amendment 2, it is assumed that the addition of PEGPH20 and atezolizumab to CIS + GEM treatment increases ORR from 26% to 66%. An ORR of 26% was observed in subjects treated with CIS + GEM combination treatment in the ABC-02 trial, a Phase 3 trial enrolling 410 patients with biliary tract cancers (Valle 2010). A total of 50 subjects, 20 each in the PEGCISGEM and PEGCISGEMATEZO treatment arms and 10 in the CISGEM arm, are required to detect a treatment difference of 40% in ORR between the CISGEM and PEGCISGEMATEZO arms with a statistical power of approximately 80% at the one-sided alpha level of 0.1.

For the cohort of approximately 15 additional subjects enrolled in the Expansion portion under Protocol Amendment 3 receiving PEGCISGEMATEZO, assuming a more conservative ORR of 60% for the PEGCISGEMATEZO treatment is observed, the 80% confidence interval is 40%, 77%. The lower bound of 40% is higher than the ORR of 37% observed in a study of the immunotherapy agent nivolumab in combination with CIS and GEM in 30 subjects with advanced biliary tract carcinoma (Ikeda 2019).

11.1.3. Analysis Populations

11.1.3.1. Enrolled Population

All subjects enrolled in the Run-in portion and the Expansion portion of the study. The Enrolled Population will be used for subject disposition, demographics, and baseline characteristics summaries.

11.1.3.2. Treated Population

All subjects in the Run-in and the Expansion portion of the study who receive any study medication. The Treated Population will be used for efficacy and safety analyses. Subjects will be analyzed based on the treatment received.

11.1.3.3. Efficacy Evaluable Population

Subjects in the Expansion portion who receive any study medication as randomized and have an evaluable baseline and post-baseline tumor assessment, unless discontinued from treatment because of disease progression or death. Efficacy Evaluable Population will be used as the primary analysis population for efficacy.

11.1.3.4. PK Analysis Population

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

11.1.4. Subject Disposition

Subject disposition data will be summarized by treatment and overall for all randomized subjects.

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

Enrollment by region and center, major protocol deviations, and the number of subjects randomized to each stratum (in Expansion only) will also be summarized.

11.1.5. Analysis of Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized using the Enrolled Population. The following demographic and baseline characteristics will be summarized: age, sex, 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 and treated population. The Efficacy Evaluable population will be the primary analysis population for efficacy. All statistical tests will be conducted at the 1-sided alpha level of 0.1. No adjustment of alpha level will be made for multiple tests.

ORR will be calculated as the number of subjects with a CR or PR divided by the number of subjects in the analysis population. For the approximately 50 subjects enrolled in the Expansion portion through Protocol Amendment 2, the treatment difference between each of the investigational arms and the control arm will be tested using the 1-sided Fisher's Exact test. Median DOR will be estimated by treatment arm using the Kaplan-Meier method. The DCR will be analyzed similarly to the ORR. For the additional cohort of approximately 15 subjects enrolled in the Expansion portion under Protocol Amendment 3 receiving PEGCISGEMATEZO, the ORR will be presented and its 80% confidence interval will be calculated using the exact method. Median DOR, DCR, and PFS in these subjects will be analyzed in a similar manner as for subjects enrolled up to Protocol Amendment 2. No statistical comparison of ORR, DOR, DCR, and PFS will be made between subjects in this additional cohort and subjects enrolled prior to Protocol Amendment 3.

PFS is defined as time from randomization to radiological disease progression or death. Kaplan-Meier method will be used to estimate the median PFS and its 80% CI, first and third quartiles, and PFS rates at Months 6, 9, and 12 by treatment arm. The PFS comparison between the PEGCISGEM and PEGCISGEMATEZO treatment arm versus CISGEM treatment arm will be based on a 1-sided log-rank test. The hazard ratio and 80% CI for the treatment effect will be estimated using the Cox proportional hazards regression model. Estimated survival curves of PFS of the three treatment arms will be displayed graphically.

OS is defined as time from randomization to death at any time. OS will be analyzed similarly as PFS.

11.1.7. Analysis of Treatment Exposure

The study medication exposure will be summarized using the Treated Population by dose level or treatment as applicable. 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

Noncompartmental analysis will be performed where possible/appropriate on PEGPH20, GEM, CIS (bound and free), and atezolizumab. The PK parameters AUC, C_{max}, C_{min}, CL, V_d, k_{el}, and $t_{1/2}$ will be summarized from noncompartmental analysis along with descriptive statistics, when applicable. Other PK analyses will be performed when appropriate.

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 endpoints.

11.1.8. Safety Analyses

All safety parameters will be summarized by treatment using the Treated Population.

All AEs will be presented in incidence tables coded by the Medical Dictionary for Regulatory Activities (MedDRA) v18.0 Preferred Term and System Organ Class. Additionally, separate AE incidence tables, coded by MedDRA, will be presented by: 1) toxicity grade (severity) graded by the CTCAE and 2) relationship to study medication (PEGPH20, CIS, GEM and atezolizumab).

In addition, subjects who experienced TE events will be summarized by Standardized MedDRA Queries (SMQ) term and MedDRA preferred term by grade.

All AEs, SAEs, 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.

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 case report forms 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.

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17. APPENDICES

APPENDIX A. 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 B. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1 (RECIST V1.1)

Selected sections from RECIST v1.1 (Eisenhauer 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.

Tumor Measurability

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

Definition of Measurable Lesions

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval ≤5 mm)

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

Definition of Non-Measurable Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with short axis ≥10 mm but <15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered

measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic Lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Methods for Assessing Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed on CT/MRI scans obtained during the screening period of the study.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation is required for this study.

Chest X-Ray

Chest CT or Chest MRI assessment of lesions are to be used in this study for radiographic response evaluation and not chest X-rays. New lesions seen on chest X-ray should be confirmed by CT or MRI (the same modality as was used at baseline/screening).

CT and MRI Scans

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scans have slice thickness of >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with prior studies, if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not,

the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, because the same lesion may appear to have a different size using a new modality.

Endoscopy, Laparoscopy, Ultrasound, Tumor Markers, Cytology, Histology

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

Assessment of Tumor Burden

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

Identification of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention because they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the CRF (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Calculation of Sum of Diameters

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, because a normal lymph node is defined as having a short axis of <10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non-lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes because they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm.

Measuring Lesions That Split or Coalesce on Treatment

When non-lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

Evaluation of Non-Target Lesions

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

Response Criteria

Criteria for Target Lesions

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

Complete Response (CR): Disappearance of all target lesions

Any pathological lymph nodes must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR

Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on or prior to the current assessment (including baseline)

In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥5 mm.

Stable Disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

Criteria for Non-Target Lesions

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedules of activities.

CR: Disappearance of all non-target lesions and (if applicable) 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 lesions and/or (if applicable) maintenance of tumor marker level above the normal limits

PD: Unequivocal progression of existing non-target lesions

Special Notes on Assessment of Progression of Non-Target Lesions

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions even in the presence of SD, PR or CR in target lesions. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of changes in non-target lesions in the face of SD, PR or CR in target lesions will be extremely rare.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not. All lymph nodes considered as new lesions must be pathological in size (≥10 mm short axis).

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

Criteria for Overall Response at a Single Timepoint

Table 13 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 13: Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (With or Without Non-Target Lesions)

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

Abbreviations: CR = complete response; NA = not applicable (i.e., no non-target lesions identified at baseline); NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

APPENDIX C. NEW YORK HEART ASSOCIATION CLASSIFICATIONS

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

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

APPENDIX D. IMMUNE-MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (IMMUNE-MODIFIED RECIST)

Conventional response criteria (e.g., standard RECIST) may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, Immune-Modified response criteria (i.e., immune-modified RECIST) have been developed to incorporate new lesions into the assessment of total tumor burden and allow radiographic progression to be confirmed at a subsequent assessment. Immune-Modified response criteria, in addition to standard RECIST v1.1, will be used to assess radiographic disease response in subjects receiving PEGCISGEMATEZO treatment.

All criteria for selecting and following target and non-target lesions are per standard RECIST v1.1 (Appendix B). The sum of diameters are calculated at baseline and each timepoint for target lesions. Tumor burden, which includes the sum of the sum of diameters of all target lesions and the sum of diameters of new target lesions (up to 5 new lesions [no more than 2 per organ]), is calculated at each post-baseline timepoint. Partial Response (PR) and progressive disease (PD) determination at each post-baseline timepoint is then based on the percent change in tumor burden from baseline (PR) or nadir (PD) as outlined in Table 14. Immune-Modified RECIST requires confirmation of PD with an additional scan obtained no sooner than 28 days after the initial scan that determined disease progression.

Immune-Modified RECIST criteria, as described within this appendix, were adapted using RECIST v1.1 (Eisenhauer 2009) by Nishino et al. (Nishino 2014), in the same manner that Immune-Related Response Criteria were adapted from WHO criteria and RECIST v1.1 by Wolchok et al. (Wolchok 2009). When not otherwise specified, RECIST v1.1 conventions will apply. Differences between Immune-Modified RECIST and RECIST v1.1 are summarized in Table 14.

Table 14: Comparison of RECIST v1.1 and Immune-Modified RECIST

	RECIST v1.1	**Immune-Modified RECIST**
Measurable new lesions	Always represent progression	Incorporated into the total tumor burden[a] and followed
Non-measurable new lesions	Always represent progression	Do not represent progression, but preclude CR
Non-target lesions	Contribute to defining CR, PR, SD, and PD	Contribute to defining CR only
CR	Disappearance of all lesions	Disappearance of all lesions
PR	≥30% decrease in sum of diameters of target lesions from baseline, in the absence of CR, new lesions, and unequivocal progression in non-target lesions	≥30% decrease in tumor burden[a] from baseline in the absence of CR
PD	≥20% increase in sum of diameters of target lesions from nadir (smallest sum of diameters on or prior to current assessment) with at least 5 mm absolute increase, unequivocal progression in non-target lesions, and/or appearance of new lesions	≥20% increase in tumor burden[a] from nadir (smallest tumor burden on or prior to current assessment) with at least 5 mm absolute increase
SD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Tumor burden is the sum of diameters of target lesions and measurable new lesions. Up to 5 new measurable lesions (no more than 2 per organ) may be selected. Tumor burden at baseline is the sum of diameters of target lesions identified at baseline.

APPENDIX E. ANAPHYLAXIS PRECAUTIONS

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observations

APPENDIX F. MANAGEMENT OF ATEZOLIZUMAB-SPECIFIC ADVERSE EVENTS