Statistical Analysis Plan

Sponsor:	Halozyme, Inc.
Protocol No:	HALO-109-202
PRA Health Sciences Project ID:	HLZPEGPH-PEGPH2
Version Date:	09DEC2016
Version Number:	2.1

APPROVALS

Sponsor Name:	Halozyme
Name of Sponsor Representative/Title:	[redacted]
Signature of Sponsor Representative /Date:	[redacted] 12DEC2016
Name of Project Manager/Title:	[redacted]
Signature of Project Manager/Date:	[redacted] 2-DEC-2016
Name of Biostatistician /Title:	[redacted]
Signature of Biostatistician /Date:	[redacted] 12-DEC-2016

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Sponsor Name:	Halozyme
Name of Sponsor Representative/Title:	[redacted]
Signature of Sponsor Representative /Date:	
Name of Project Manager/Title:	
Signature of Project Manager/Date:	2-DEC-2016
Name of Biostatistician /Title:	
Signature of Biostatistician /Date:	12-DEC-2016

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Sponsor Name:	Halozyme
Name of Sponsor Representative/Title:	[redacted]
Signature of Sponsor Representative /Date:	
Name of Project Manager/Title:	[redacted]
Signature of Project Manager/Date:	
Name of Biostatistician /Title:	[redacted]
Signature of Biostatistician /Date:	

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected during the Phase 2, randomized, multicenter study of PEGPH20 (PEGylated Recombinant Human Hyaluronidase) combined with nab-paclitaxel (NAB) plus gemcitabine (GEM) compared with nab-paclitaxel plus gemcitabine in subjects with stage IV untreated pancreatic cancer under Halozyme, Inc. protocol HALO-109-202.

This SAP should be read in conjunction with the study protocol and the case report forms (CRF). This version of the SAP has been developed using the protocol dated 06APR2015 and CRFs dated 24FEB2016. Any further changes to the protocol or the CRFs may necessitate updates to the SAP.

The SAP will be developed in 2 stages, SAP1 and SAP2. The purpose of this 2 stage process is to have SAP1 "finalized" so that programming can be initiated earlier in the process. Until initial sponsor approval, the SAP will be known as SAP1. Changes following approval of SAP1 will be tracked in a SAP Change Log and a final version of the SAP, SAP2, will be issued for sponsor approval prior to database lock.

1.1 CHANGES FROM PROTOCOL

Changes and clarifications have been made in this final SAP from the protocol amendment 5 dated 06APR2015. The changes and rationales are summarized below:

1) The data cut-point for the final PFS analysis is changed from the time point when 182 PFS events have occurred to the time point when at least 95% of subjects enrolled and at least 95% of subjects with high HA level have discontinued from treatment. The rationale for this change is the low likelihood of achieving 182 PFS events based on a higher than anticipated discontinuation rate in Stage 1 of the study for reasons other than progressive disease (e.g. adverse events, withdrawal of consent, and investigator decision) and that once a subject discontinues study treatment, the subject enters a long-term follow-up period, where only survival status and post-treatment therapy data are collected, and no other study procedures, including CT scans, are conducted. An administrative letter on this change has been issued to all investigator sites and IRBs on 24MAR2016.
2) The PFS event definition for deaths has been clarified from deaths from any cause while on study treatment to deaths from any cause that occur within 14 days of the last dose of study treatment. The rationale for adding 14 days to the last study treatment dose date is that the dosing interval between cycles without a dose is 14 days per protocol. The rationale for not considering deaths that occur longer than 14 days after the last study treatment as PFS events is that no disease assessments are conducted when a subject is in long-term follow up after treatment discontinuation.
3) The efficacy analysis for Stage 2 will be conducted using the Safety Population defined as all subjects who receive a study treatment dose. The rationale for this change from the previously defined efficacy evaluable population for Stage 2 efficacy analyses is to take a more conservative approach to analyze Stage 2 efficacy data by including all subjects who received a study treatment dose. The efficacy evaluable population was more restrictive as it required subjects to have been dosed and had at least one post-baseline tumor assessment, experience clinical progression, or die within 14 days of last dose.
4) The censoring rule for the primary PFS endpoint of censoring subjects for PFS if they experience a thromboembolic (TE) event in Stage 2 was removed. The rationale for this change is to take a more conservative intent-to-treat approach where all data under the randomized treatment are

included in the PFS analysis. Per protocol, subjects who experience any TE are discontinued from PEGPH20 treatment, but AG treatment may continue. The previous censoring rule was put in place given that the PAG treatment effect may be diluted by AG treatment only being given after a TE event occurs. This censoring rule is now removed.

5) Information regarding the statistical powering assumptions is being added for the Stage 2 prospectively defined HA-high subgroup of subjects. The rationale for this addition is to prospectively define the statistical powering used for validating the retrospectively defined HA algorithm and cut-point of 50 (≥ 50 for HA-high), which was developed based on Stage1 efficacy data.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

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

2.2 SECONDARY OBJECTIVES

Secondary objectives for this study are:

- To estimate the relative benefit of PAG treatment versus treatment with nab-paclitaxel plus gemcitabine (AG treatment), as assessed by the PFS hazard ratio.
- To estimate the relative benefit of PAG treatment versus AG treatment, as assessed by the PFS hazard ratio based on subject tumor-associated hyaluronan (HA) levels.
- To estimate the objective response rate (ORR), as defined by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), of PAG treatment and the relative benefit of PAG treatment versus AG treatment.
- To estimate the overall survival (OS) duration of PAG treatment and the relative benefit of PAG treatment versus AG treatment, as assessed by the OS hazard ratio.
- To evaluate the safety and tolerability profile of the PAG and AG treatment groups.
- To characterize the plasma pharmacokinetics (PK) of PEGPH20 when given in combination with NAB plus GEM.

2.3 EXPLORATORY OBJECTIVES

Exploratory objectives for this study are:

- To estimate the OS benefit of PAG treatment versus AG treatment based on HA levels from tumor biopsies.
- To estimate the duration of response (DOR) of responders (complete response [CR] and partial response [PR]) in the PAG and AG treatment groups.
- To compare the disease control rate (DCR; CR, PR and stable disease [SD]) between the PAG and AG treatment groups.

- To compare CA19-9 changes between the PAG and AG treatment groups.
- To assess treatment effect of PAG with regard to HA levels in plasma and in tumor biopsies.

3. STUDY DESIGN

This is a Phase 2, multi-center, open-label, randomized study of PAG treatment compared with AG treatment in subjects with Stage IV previously untreated pancreatic cancer. The study has two run-in phases, one for each formulation of PEGPH20 (original and new formulations). The first run-in phase was initiated before Phase 2 and will evaluate the safety and tolerability of PAG treatment (original PEGPH20 formulation) compared with AG treatment. The Phase 2 portion is an open label randomized study and has two stages. With Amendment 1, a second run-in phase will be conducted to incorporate a new formulation of PEGPH20 during Phase 2. Stage 2 of the Phase 2 portion was added in Protocol Amendment 3 after the clinical hold. The dosing schedule for subjects randomized to the PAG and AG treatment groups will be the same in the run-in phases and Phase 2 (see Section 6.1.3 of the final protocol dated 06APR2015). The treatment period will consist of 4-week treatment cycles (28 days) with Week 4 of every cycle as a rest week (i.e., no treatment will be given). Treatment will continue until disease progression or unacceptable toxicity, or until the subject is withdrawn from the study for any reason, whichever comes first.

3.1 RUN-IN PHASES

3.1.1 Original formulation of PEGPH20

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

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

3.1.2 New Formulation of PEGPH20

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

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

3.2 PHASE 2

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

Phase 2 has 2 stages: Subjects will be randomized to receive PAG or AG treatment in a 1:1 ratio in Stage 1 and in a 2:1 ratio in Stage 2. The second stage of the study starts with protocol amendment 3.0.

Effective with amendment 3.0, all active subjects will be treated with prophylactic doses of enoxaparin (40 mg daily). Enoxaparin treatment should start immediately following the consent for amendment 3.0 for ongoing subjects and Day 1 for new subjects entered into the trial. Effective with amendment 4.0, all active subjects will be treated with enoxaparin at 1 mg/kg/day. Enoxaparin should start immediately following consent for amendment 4.0 for ongoing subjects and on Day 1 for new subjects entered into the trial thereafter.

3.2.1 PAG Treatment Group

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

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

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

3.2.2 AG Treatment Group

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

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

See final protocol, Section 6.1.3.2, for details on study medication schedules. The schedule of events at screening for the PAG and AG treatment groups is in Table 1 and the schedules of events after screening for the PAG treatment and AG treatment groups are in Table 2 and Table 3, respectively. The PK and HA sample collection times for the run-in phase and Phase 2 are in Table 4 and Table 5, respectively. An overview of study medication schedule by treatment group is in Table 6.

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

Tests and Assessments[a]	Screening		
	≤20 Days Prior to D1	≤14 Days Prior to D1	≤7 Days Prior to D1
Sign and Date ICF	X		
Confirm Availability of Tumor Tissue[b]	X[b]		
Subject Registration/Randomization		X	
Medical History	X		
Physical Examination		X[c]	
Vital Signs		X[c]	
Karnofsky Performance Status		X	
Height		X[c]	
Weight/BSA		X[c]	
Disease Assessment (CT) [d]	X[c]		
Doppler Ultrasound of lower extremities		X	X
Local Laboratory Tests			
Urine/Serum Pregnancy Test (female subjects of reproductive potential)		X	
Central Laboratory Tests			
Hematology		X	
Blood Chemistry		X	
Urinalysis		X	
Coagulation Tests (PT, PTT, INR)		X	
CA19-9		X	
Plasma HA levels		X	
Prior Medication History	X		

Abbreviations: AG = nab-paclitaxel+gemcitabine; BSA = body surface area; CT = computed tomography; D1 = Study Day 1; HA = hyaluronan; ICF = Informed Consent Form; INR= international normalized ratio; PAG = PEGPH20 in combination with nab-paclitaxel+gemcitabine; PT = prothrombin time; PTT = partial thromboplastin time.

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

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

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

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

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

	Treatment Cycle 1 (4 Weeks)								Treatment Cycles 2+ (Repeats every 4 weeks)				End of Treatment[b]	Long-term Follow-up
	Wk1			Wk2		Wk 3		Wk 4	Wk1	Wk2	Wk 3	Wk 4		
Test and Assessments[a]	**D1**	**D2**	**D4**	**D8**	**D11**	**D15**	**D18**	**D22**	**D1**	**D8**	**D15**	**D22**		
Physical Examination	X								X				X	
Vital Signs	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X	X[c]	X[c]	X[c]	X	X	
Karnofsky Performance Status	X								X				X	
Weight/BSA	X								X				X	
12-lead ECG[d]	X					X								
Disease Assessment (CT)												X[e]	X[f]	
Central Laboratory Tests														
Hematology	X			X		X		X	X	X	X	X	X	
Blood Chemistry	X			X		X		X	X	X	X	X	X	
Immunogenicity	X[g]								X[g]				X	
CA19-9								X				X	X	
PK & HA levels	Refer to Table 4 and Table 5 for schedule for PK & HA sampling timepoints													
PEGPH20 Administration	X		X	X	X	X	X		X	X	X			
Coagulation Testing (PT, PTT, INR- Local Lab)	X			X		X		X	X	X	X	X	X	
Dexamethasone Administration[h]	X		X	X	X	X	X		X	X	X			
Nab-paclitaxel Administration		X[i]		X[j]		X[j]			X[j]	X[j]	X[j]			
Gemcitabine Administration		X[i]		X[j]		X[j]			X[j]	X[j]	X[j]			
Optional Post-dose Tumor Biopsy[l]								X				X		
Concomitant Therapy and Procedure Recording	X												X	
Adverse Event Recording	X												X	
Long-term Follow-up[l]														X

Footnotes overleaf.

Abbreviations: BSA = body surface area; CT = computed tomography; D = day; ECG = electrocardiogram; HA = hyaluronan; INR = international normalized ratio; PAG = PEGPH20 in combination with nab-paclitaxel+gemcitabine; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time.

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

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

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

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

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

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

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

[h] Dexamethasone should be given within 2 hours prior to the start of each PEGPH20 dose and 8-12 hours after each PEGPH20 dose.

[i] Nab- paclitaxel and gemcitabine will be given 24 hours (±4 hours) after the dose of PEGPH20. Nab-paclitaxel will be given first.

[j] Nab-paclitaxel and gemcitabine will be given 2 to 4 hours after the PEGPH20 dose. Nab-paclitaxel will be given first.

[k] Optional post-dose tumor biopsy may be done anytime in Week 4 of Cycle 1. See protocol Section 8.2.10 for tissue requirements.

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

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

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

Abbreviations: AG = nab-paclitaxel+gemcitabine; BSA = body surface area; CT = computed tomography; D = day; ECG = electrocardiogram; HA = hyaluronan; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time.

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

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

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

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

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

[f] CT should only be done if radiologic progressive disease was not documented in the previous CT scan.
[g] HA level plasma sample should be drawn prior to the first nab-paclitaxel dose in each cycle.
[h] Dexamethasone should be given within 2 hours prior to each nab-paclitaxel dose and 8-12 hours post each gemcitabine dose.
[i] Nab-paclitaxel will be given first, followed by gemcitabine.
[j] Optional post-dose tumor biopsy may be done anytime in Week 4 of Cycle 1. See the protocol, Section 8.2.10, for tissue requirements.
[k] After the End of Treatment Visit, subjects will enter long-term follow up during which information on the subject's survival will be obtained by the site on a monthly basis. In addition, efforts should be made to collect data on the subject's next anti-cancer therapy on a monthly basis. Long term follow-up will continue until the subject dies, is lost to follow-up, or withdraws consent.

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

	Treatment Cycle 1 (4 Weeks)								Treatment Cycles 2+ (Repeats every 4 weeks)			
	Week1			Week2		Week 3		Week 4	Week1	Week2	Week 3	Week 4
Test and Group	D1	D2	D4	D8	D11	D15	D18	D22	D1	D8	D15	D22
PK and HA Sample Collection[a]	X[b]	X[c]	X[d]	X[e]	X[d]	X[b]	X[d]		X[f]	X[d]		

Abbreviations: D = day; HA = hyaluronan; PAG = PEGPH20 in combination with nab-paclitaxel+gemcitabine; PK = pharmacokinetics.
[a] Windows for blood draws: Pre-dose: within 2 hours of dosing. Post-dose: 15 minutes ±5 minutes, 1 hour (±15 minutes), 2 hour (±15 minutes), 4 hour (±30 minutes).Post gemcitabine= within 2 hours of completion of gemcitabine administration.
[b] PK: Pre-PEGPH20 dosing, and 15 minutes, 1 hour, 2 hours, and 4 hours post-PEGPH20 dosing. A Cycle 1 Day 15, 24 hour post-dose sample is optional.
HA**:** Pre-PEGPH20 dose (Day 1 only).
[c] PK and HA: 24 hours post-PEGPH20 dose (±4 hours) and prior to nab-paclitaxel dose.
[d] PK: Pre-PEGPH20 dose and 1 hour post-PEGPH20 dose.
[e] PK: Pre-PEGPH20 dose and 1 hour post-PEGPH20 dose, and immediately after gemcitabine dose.
[f] HA: Collect 1 HA sample pre-PEGPH20 and a second HA sample after gemcitabine administration.

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

	Treatment Cycle 1 (4 Weeks)								Treatment Cycles 2+ (Repeats every 4 weeks)			
	Week1			Week2		Week 3		Week 4	Week1	Week2	Week 3	Week 4
Test and Group	D1	D2	D4	D8	D11	D15	D18	D22	D1	D8	D15	D22
PK and HA Sample Collection[a]	X[b]	X[c]				X[d]			X[e]	X[f]		

Abbreviations: D = day; HA = hyaluronan; PAG = PEGPH20 in combination with nab-paclitaxel+gemcitabine; PK = pharmacokinetics. Post gemcitabine= within 2 hours of completion of gemcitabine administration.
[a] Windows for blood draws: Pre-dose: within 2 hours of dosing. Post-dose: 1 hour (±15 minutes).
[b] PK: Pre-PEGPH20 dose and 1 hour post-PEGPH20 dose. HA: Pre-PEGPH20 dose.
[c] PK and HA: 24 hours post-PEGPH20 dose (±4 hours) and prior to nab-paclitaxel dose.
[d] PK: Pre-PEGPH20 dose and 1 hour post-PEGPH20 dose.
[e] HA: Collect 1 HA sample pre-PEGPH20 and a second HA sample after gemcitabine administration.
[f] PK: Pre-PEGPH20 dose and 1 hour post PEGPH20 dose.

Table 6: Overview of Study Medication Schedule by Treatment Group

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

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

3.3 SAMPLE SIZE CONSIDERATIONS

Approximately 16 subjects with newly diagnosed, previously untreated Stage IV pancreatic cancer will be randomized in a 3:1 ratio to receive either PAG or AG treatment in the run-in Phases; approximately 8 of these subjects will be randomized in a 3:1 ratio to receive either the original formulation of PEGPH20 in combination with NAB+GEM or AG treatment, and approximately 8 of these subjects will be randomized in a 3:1 ratio to receive either the new formulation of PEGPH20 in combination with NAB+GEM or AG treatment.

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

One hundred twenty-three subjects with newly diagnosed, previously untreated Stage IV pancreatic cancer will be randomized in a 1:1 ratio to either the PAG or AG treatment group in Stage 1 of the Phase 2 portion of the study.

In Stage 2 of Phase 2 of this study, 114 subjects will be randomized in a 2:1 ratio to receive PAG or AG treatment: 76 subjects in the PAG arm and 38 subjects in the AG arm.

At the time of this SAP sign-off, enrollment has been completed for this study. A total of 279 subjects were enrolled and randomized in this study: 146 subjects in Stage 1 (23 subjects in two run-in phases and 123 subjects in Stage 1 of Phase 2) and 133 subjects in Stage 2.

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

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

Four interim safety analyses of thromboembolic events will be conducted using the stopping boundary of the one-sided p-value of 0.05 for the first two analyses and 0.035 for the remaining two analyses based on the Pocock method (Pocock, 1977).

If the thromboembolic rate of 23% is assumed, the sample size of 76 subjects in the PAG arm at Stage 2 would provide an overall statistical power of approximately 90% to reject the null hypothesis and declare that the incidence rate of thromboembolic events in subjects treated with PAG is greater than 12% at the significance level of 0.1 based on the one-sided Z test.

It was initially expected that 237 subjects in Phase 2 will be enrolled in approximately 20 months and these subjects will be followed up for an additional 15 months. There will be approximately 200 subjects, including subjects from both run-in phases, in the Efficacy Evaluable Population for the primary comparisons. It is estimated that the median PFS time is 5.5 months for AG treatment (Von Hoff, 2013). A sample size of 100 evaluable subjects per treatment group with a total of 182 PFS events (disease progression or death) will provide 80% statistical power to detect a 45% treatment effect in median PFS (5.5 months for AG versus 8 months for PAG) based on the two-sided log-rank test at the significance level of 0.1. In addition, a total of 200 subjects with 160 deaths will provide 80% statistical power to detect 40% benefit in median OS (8.5 months for AG versus 11.9 months for PAG) at one-sided alpha level of 0.1. Assuming 35% of subjects have tumors with high HA content, the study has 80% statistical power for the high HA subgroup to detect 90% benefit in median PFS (5.5 months for AG versus 10.5 months for PAG) at two-sided alpha level of 0.1 and 80% benefit in median OS (8.5 months for AG versus 15.3 months for PAG) at one-sided alpha level of 0.1.

The study was initially powered with 182 PFS events for the primary efficacy endpoint of PFS with 80% statistical power at significance level of 0.1, as shown above. The final analysis of PFS was expected to be conducted when 182 PFS events had occurred.

According to the data of Stage 1 of the study, greater than 35% of subjects have discontinued from study treatment due to reasons other than disease progression, such as adverse events, withdrawal of consent, and investigator decision. Thus, a total of 182 PFS events is unlikely to be achievable in this study. In order to ensure maturity of the final PFS analysis, the final analysis of PFS will be conducted when at least 95% of the total number of subjects enrolled and when at least 95% of subjects with high HA level have discontinued from study treatment.

After a subject has discontinued from study treatment, the subject enters a long-term follow-up period. During the study long-term follow-up, only survival status and post-treatment therapy data will be collected, and no other study procedures, including CT scans, will be conducted, thus, no additional information will available for PFS assessment after a patient has discontinued from study treatment.

Efficacy data from Stage 1 were utilized to develop the HA algorithm and cut-point by Ventana Medical Systems. The HA score of 50 was selected as the cut-point to define HA-high (≥ 50) and HA-low (< 50), which was outlined further in the submitted and approved investigational device exemption (IDE). The efficacy data from Stage 2 will be used to prospectively validate the HA algorithm and cut-point of 50. The sponsor will remain blinded, as outlined in Appendix 5, to PFS, ORR, and HA data until the database is locked and the final analyses are complete. The HA testing of Stage 2 is yet to begin but is planned to begin in May 2016. The prevalence of HA high subjects was approximately 36% (43/118, which was

determined retrospectively based on biopsy samples collected in subjects enrolled in Stage 1), thus the anticipated number of HA high subjects in Stage 2 is approximately 39. Given the 2:1 randomization, it is expected that, in the Stage 2 analysis population for HA high cut-point validation, approximately 26 HA-high subjects in the PAG arm and 13 HA high subjects in the AG arm will be available. A total of 20 PFS events from 39 HA-high subjects will have a statistical power of approximately 83%, 70%, and 56% to detect a statistically significant PFS benefit for PAG treatment with hazard ratio (HR) of 0.4, 0.5, and 0.6 respectively at 1-sided alpha level of 0.15.

3.4 RANDOMIZATION

This study plans to randomize approximately 253 subjects (inclusive of two run-in phases and two stages of phase 2).

Original Run-in and New Formulation Run-in Phases: In each run-in phase, approximately 8 subjects will be randomized in a 3:1 ratio to receive PEGPH20 (3.0 µg/kg) in combination with standard dosing of NAB+GEM (PAG treatment) or NAB+GEM (AG treatment). No stratification factors will be used. Additional subjects may be enrolled to further assess the tolerability of PEGPH20 in order to establish the acceptable safety profile prior to the randomization of Phase 2 of the study. For the original run-in phase, the randomization numbers are from 101 to 110; and for the new formulation run-in phase, the randomization numbers are from 181 to 199.

Phase 2: 123 subjects with newly diagnosed, previously untreated Stage IV pancreatic cancer will be randomized in a 1:1 ratio to either the PAG or AG treatment group in Stage 1 of the Phase 2 portion of the study. In Stage 2 of the Phase 2 portion of the study, 114 subjects will be randomized in a 2:1 ratio to receive PAG or AG treatment: 76 subjects in the PAG arm and 38 subjects in the AG arm. Randomization will be stratified by the Karnofsky performance status (KPS) category at screening. For the purpose of the analyses mentioned in this analysis plan, in defining KPS categories, KPS scores at screening collected on eCRFs will be pooled to form two categories; 70 & 80% vs. 90 &100%. If the screening KPS score is missing for a subject, baseline score will be used. Any KPS score <70% will be pooled in the 70-80% category.

For Phase 2 Stage 1, the randomization numbers are from 201-599; and for Phase 2 Stage 2, the randomization numbers are from 697-996.

4. STUDY VARIABLES AND COVARIATES

4.1 PRIMARY VARIABLES

The primary variables are:

- PFS (measured from the date of randomization until disease progression or death from any cause)
- The thromboembolic events in subjects treated in the PAG arm in Stage 2 of the study

4.2 SECONDARY VARIABLES

The secondary variables for the study are:

- PFS.
- PFS in relation to HA levels.
- ORR (defined as the percentage of subjects with a RECIST v1.1 PR or CR).

- OS (measured from the date of randomization until death from any cause).
- Safety endpoints.
- Plasma pharmacokinetics (PK) of PEGPH20 when given in combination with NAB plus GEM.

4.3 EXPLORATORY EFFICACY VARIABLES

The exploratory efficacy endpoints for the study are:

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

4.4 PREDETERMINED COVARIATES AND PROGNOSTIC FACTORS

This study includes two KPS categories (scores 70 & 80% as one category and 90 &100% as another category) used as randomization stratification factors and HA as a covariate. The KPS category will be used as the stratification variable when performing stratified analysis. HA level may be included in the analysis model as a covariate as well.

5. DEFINITIONS

Baseline

Baseline is defined as the last measurement prior to dosing on Day 1 of Cycle 1. Baseline measurements will generally be taken on Cycle 1 Day 1. If parameters are not measured prior to dosing on Day 1 in Cycle 1, such as vital signs, then the most recently measured values prior to Cycle 1 Day 1 within 14 days will be considered baseline. For subjects who are randomized but not dosed after the randomization, the baseline is defined as the last measurement prior to or on the date of randomization.

Body Surface Area (BSA)

Body surface area is calculated using the Dubois formula:

$$BSA\ (m^2) = Weight\ (kg)^{0.425} \times Height\ (cm)^{0.725}) \times 0.007184$$

Study Medication

Study medications are defined as PEGPH20, gemcitabine, and nab-paclitaxel.

First Dose Date

The first dose date is defined as the date of first dose of any study medication.

Weight-adjusted Cumulative Dose

The weight-adjusted cumulative dose administered for PEGPH20 is defined as:

Sum of (dose administered at a given visit / the subject's most recent weight measurement before the infusion).

BSA-adjusted Cumulative Dose

The BSA-adjusted cumulative dose administered for chemotherapy regimen (nab-paclitaxel, gemcitabine) is defined as:

Sum of (dose administered at a visit / the subject's most recent BSA). Where BSA for each dose is based on the subject's most recent weight before infusion and calculated by the Dubois formula.

Actual Dose Intensity (ADI)

The actual dose intensity for each study therapy is the weight- or BSA-adjusted cumulative dose divided by the duration of exposure in cycles of 28 days for each study therapy. Scheduled drug administration visits that are missed (actual dose received is set to be 0), or dose-reduced, will be included in the calculation of ADI.

Relative Dose Intensity (RDI)

Relative dose intensity in percent will be defined as:

$$\frac{\text{Sum of (adjusted cumulative dose within each cycle/planned adjusted dose for the cycle)}}{\text{Actual duration of exposure in cycles}} \times 100$$

Where Actual duration of exposure in cycles is defined as:

$$\left(\frac{\text{first dose date of last cycle of any study drug - first dose date of first cycle of any study drug}}{28}\right)+1$$

and the planned adjusted dose for each cycle is shown in Table 7 below.

Table 7: Planned Adjusted Dose for Study Medications

Drug	Planned Adjusted Dose	
	Cycle 1	Cycle 2 and after
PEGPH20	18 µg/kg	9 µg/kg
Nab-paclitaxel	375 mg/m^2	375 mg/m^2
Gemcitabine	3000 mg/m^2	3000 mg/m^2

Overall Objective Response

The overall objective response is equivalent to the best overall response per RECIST criteria v1.1 (Appendix 4) which is the best response recorded from enrollment until disease progression during the treatment phase.

A tumor response based on imaging scans is determined by considering the radiological assessments of target and non-target lesions, and evidence of new lesions according to RECIST v1.1 (Appendix 4). A subject's overall objective response is derived from the sequence of tumor responses (scheduled and unscheduled) during the treatment phase. All tumor responses will be reviewed by central radiologists and the data will be transferred and entered through electronic data entry by the central radiologists directly. Assessments based on central radiology will be used in the key analyses and additional exploratory analyses based on investigator disease assessment may be repeated.

Overall Response Rate (ORR)

The Overall Response Rate is the subject incidence of an overall objective response of CR or PR. The objective responses do not need confirmation.

On-Study Treatment Period for Collection of Adverse Events

Any adverse event occurring from first dose date to 30 days after last dose date is defined as on-study.

Change from Baseline

Change from baseline is defined as (value at post-baseline visit – value at baseline). If the baseline or post-baseline value is missing, then the change from baseline is set to missing.

Concomitant and Prior Medication

All medication administered within 20 days prior to the first administration of study medication through the later of the End of Treatment Visit or 30 days after the last dose date will be recorded on the Concomitant Medication electronic case report form (eCRF). Prior medications are defined as medications with a start date prior to first dose of study medication. Concomitant medications are defined as any medications ongoing at the start of treatment or with a start date on or after the date of first study medication dose at study Day 1 in Cycle 1.

Month:

A time period in months will be calculated as (12/365.25)*(number of days of interest in the period).

Duration of Response (DOR)

Duration of Response is defined as duration (in months) from the first date of response (PR or CR) to date of first progression of disease (RECIST v1.1) in the subset of subjects with an objective response of CR or PR. Subjects who respond and have not progressed while on study will be censored at the date of their last evaluable tumor assessment. Duration of response is calculated only for subjects with an objective response.

Date of Last Contact

Date of Last Contact is defined as the latest date on which the subject was known to be alive or the date of death for subjects known to have died.

Progression-Free Survival Time (PFS)

Progression-Free Survival Time is defined as the duration (in months) from the date of randomization to the date of radiographic disease progression (RECIST v1.1), clinical disease progression assessed by investigator or death during the treatment period from any cause. Treatment period is defined as randomization date through 14 days after the last dose of any study medication. Deaths occurring after 14 days of the last dose date without disease progression will not be considered as PFS events. Subjects with missing protocol scheduled tumor assessment(s) prior to radiologic disease progression will be considered as having disease progression on the date of the actual assessment of disease progression. Subjects not meeting the criteria are censored at the last evaluable tumor assessment date. Subjects who are alive during the treatment phase with no post-baseline tumor assessments, will be censored at the date of randomization for the purpose of PFS calculations.

Disease Control Rate (DCR)

DCR is defined as the incidence of an overall objective response of CR, PR or SD. A best response of SD must be at least 6 weeks after first dose date.

Overall Survival (OS)

Overall Survival is the interval (in months) from the date of randomization to the date of death. Subjects who have not died or are lost to follow-up by the date of analysis data cutoff will be censored at their last contact date.

Corrected QT Interval (QTcF)

QTcF is defined as corrected QT interval with Fridericia's correction formula: $QTcF=QT/(RR)^{1/3}$, where QT is the heart rate interval, measured in milliseconds and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, measured in seconds.

Treatment-emergent AE:

Treatment-emergent AEs are those that first occur or increase in severity after the first dose of study medication and not more than 30 days after the last dose of study medication, and/or any treatment-related AE regardless of the onset date.

Treatment-related AE

A treatment related AE is an event that is related to PEGPH20, NAB, or GEM (assessed as "Yes, Related," "Probably Related," or "Possibly Related") as reported on an AE eCRF for any subject whom had taken at least 1 dose of the above study therapy.

- PEGPH20-related: an AE assessed as 'Yes, Related', 'Probably Related', or 'Possibly Related' for the eCRF question 'Is this event related to PEGPH20?'.
- Nab-paclitaxel-related: an AE assessed as 'Yes, Related', 'Probably Related', or 'Possibly Related' for the eCRF question 'Is this event related to Nab-Paclitaxel?'.
- Gemcitabine-related: an AE assessed as 'Yes, Related', 'Probably Related', or 'Possibly Related' for the eCRF question 'Is this event related to Gemcitabine?'.

Incidence rate per subject-year (IR per subject-year)

The IR per subject-year is the number of subjects with events divided by the total number of subject-years within the subjects that are on the study.

6. POPULATIONS

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

Efficacy Evaluable (EE) Population: All randomized subjects who receive at least 1 dose of any study medication, including the run-in phases, who have measurable disease at baseline, and have a post-baseline response assessment, or have clinical disease progression without a post-baseline CT scan, or have died on or prior to 14 days after the last dose date, will be included in the overall Efficacy Evaluable Population. The Efficacy Evaluable Population will be used as the primary analysis population for the overall (Stage 1 + Stage 2) efficacy analyses.

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

Safety Population of Stage 1: A sub-population of the Safety population for subjects enrolled in Stage 1 of the study, including two run-in phases and Stage 1 of Phase 2 before the clinical hold. The Safety Population of Stage 1 will be used for analyses of efficacy and thromboembolic events of Stage 1 of the study. Subjects will be grouped according to the actual treatment received.

Safety Population of Stage 2: A sub-population of the Safety population for subjects enrolled in Stage 2 of Phase 2 of the study after the clinical hold. The Safety Population of Stage 2 will be used for analyses of all efficacy and safety data of Stage 2 of the study. This is the analysis population for the primary safety endpoint. Subjects will be grouped according to the actual treatment received.

CA19-9 Evaluable Population: All subjects who have a baseline value higher than 59xULN (upper limit normal: 37mg/dL) and at least one post-baseline assessment will be included in the CA19-9 evaluable population. The CA19-9 evaluable population will be used for the analysis of CA19-9 change from baseline.

HA-level Subgroup: All efficacy analysis will be conducted based on the HA score category (HA-high and HA-low) for the ITT population, EE population, Safety population, Safety population of the Stage 1, and Safety population of the Stage 2.

The Stage 1 data were used to develop the HA cut-point to define HA-high subgroup of subjects (HA score ≥ HA cut-point) and HA-low subgroup of subjects (HA score < HA cut-point). This cut-point will be used to prospectively define HA-high or HA-low subgroups of Stage 2 safety population in order to validate the cut-point.

In addition, for subjects with more than one HA assessment score, the highest HA score will be used to define HA subgroups.

Initial Enoxaparin Dosing Subgroups: Thromboembolic adverse events will also be summarized for the following two subgroups;

1. Safety Population of Stage 2 – Subjects Enrolled Under Protocol Amendment 3 and Received an Initial Prophylactic Enoxaparin Dose of 40 mg.

Note that effective with protocol amendment 3.0, all active subjects on both arms were to be treated with prophylactic doses of enoxaparin (40 mg daily) immediately following consent.

2. Safety Population of Stage 2 – Subjects Enrolled under Protocol Amendment 3 and Received an Initial Prophylactic Enoxaparin Dose Other than 40 mg or Subjects Enrolled under Protocol Amendment 4 or Later.

Effective with protocol amendment 4.0, all subjects on both arms were to be treated with enoxaparin at a dose of 1 mg/kg/day immediately following consent.

7. INTERIM ANALYSES

No formal interim analyses for efficacy are planned for this study. The participating Investigators, the Sponsor, and the independent safety physician will review the safety profile of all subjects in the run-in phases and determine that the defined dose and regimen are acceptable for Phase 2.

In addition, after the initiation of the Phase 2 portion, the Data Monitoring Committee (DMC) will review aggregated safety data collected to-date on a periodic basis. Safety data include AEs, laboratory data, and other safety clinical observations. Efficacy data will not be reviewed by the DMC unless there are safety concerns to warrant a risk versus benefit assessment. Details of the DMC (analysis, frequency, etc.) will be captured in a separate charter.

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

In Stage 2 of this study, three interim safety analyses are planned to monitor thromboembolic risk. If any of the interim safety analyses crosses the stopping boundary, the study may be terminated. The DMC may recommend terminating the study. For subjects in Stage 1 who are eligible to re-initiate PEGPH20 treatment, an interim analysis will be conducted after the last re-entry subject has had one cycle of PAG

treatment or has discontinued from treatment during the first treatment cycle after re-entry. If the TE rate exceeds 25%, all re-entry subjects will be discontinued from PEGPH20 treatment.

The Stage 1 efficacy data were analyzed to develop the HA algorithm and cut-point to define HA-high subjects. The HA cut-point will be prospectively applied to Stage 2 data for validating the HA algorithm and cut-point developed from Stage 1 data.

8. DATA REVIEW

Final data for analysis will be cleaned prior to receipt by PRA Health Sciences Analysis and Reporting. Ongoing data handling will take place by the study programmer and the independent statistician, until the time at which the study team has full access to the data. The purpose of this section is to indicate the history of the data and the process used to ensure that the data are acceptable for statistical analysis prior to database lock.

8.1 DATA HANDLING AND TRANSFER

All of the data will come from the PRA Health Sciences data management group and be extracted in SAS® dataset format (SAS v9.1 or later) and converted to SDTM v3.1.2. Please refer to the Data Management Plan for details.

8.2 DATA SCREENING

Beyond the data screening called for in the PRA Health Sciences Data Management Plan, the PRA Health Sciences programming of analysis datasets, tables, figures, and listings (TFLs) also provides data screening. Presumed data issues will be output into a spreadsheet and sent to Data Management.

Review of a pre-freeze TFLs run on clean subjects and a post-freeze TFLs run on the frozen database allow for further data screening prior to lock. The post-freeze TFLs will be discussed with the sponsor in a data review meeting to identify any final data issues and seek corrections, as necessary, prior to database lock. The PRA Health Sciences biostatistician and the sponsor must approve database lock.

9. STATISTICAL METHODS

In general, categorical data will be summarized using number of subjects (n), frequency, and percentages, with the denominator for percentages being the number of subjects in the study population for each treatment group unless otherwise specified. Percentages will be rounded to 1 decimal place except for 100%, which will have no decimal place.

Continuous data will be summarized using the number of subjects, mean, standard deviation, median, quartiles (Q1, Q3), minimum, and maximum. The mean, median, and quartiles (Q1, Q3) will be presented to 1 decimal place greater than the original data; the standard deviation will be presented to 2 decimal places greater than the original data; and the minimum and maximum will have the same number of decimal places as the original data.

Results will be displayed for the 2 treatment groups as well as the 2 groups combined (total). All statistical analyses and data listings will be performed using SAS® software version 9.3 or higher.

9.1 SUBJECT DISPOSITION

Subject disposition data (including analysis population and time on study treatment) will be summarized for all randomized subjects. The total number of subjects who completed Phase 2 as well as the overall number of subjects will also be presented. The number and percentage of subjects who discontinued the

study early and a breakdown of the corresponding reasons for withdrawal will be summarized. In addition, all subject disposition data will be presented in a listing.

9.2 PROTOCOL DEVIATIONS AND VIOLATIONS

Important protocol deviations (i.e., violation) include substantial departures from protocol guidelines that might affect treatment comparisons, the analysis of stated objectives, or subject safety. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented. All important deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment will be summarized in a table and all the protocol deviations including important protocol deviations will be presented in a listing. The subject data listing will be sorted by treatment group and subject number.

9.3 TREATMENTS

9.3.1 Extent of Study Medication Exposure

Cycles are identified by visit code on the eCRF, and this will be used to define dosing cycle for summaries. Cycle start date will be defined as the first dose date within a cycle and cycle stop date will be defined as the day before first dose date of the next cycle. Stop date of last cycle is defined as the earliest of the first dose date of last cycle + 27 days, the data cutoff date, or the EOT date for discontinued subjects. Cycles should last 28 days. The following summary statistics will be calculated:

- Cumulative dose summed across all cycles per subject. For PEGPH20, we also define cumulative dose within Cycle 1 as cumulative dose summed before the first dose date of Cycle 2 and define cumulative dose after Cycle 1 on or after the first dose date of Cycle 2.
- Adjusted cumulative dose for PEGPH20 is defined as Weight-adjusted Cumulative Dose. For NAB and GEM, adjusted cumulative dose is defined as BSA-adjusted Cumulative Dose. (See Section 5).
- Actual duration of exposure (in cycles) is defined as [(first dose date of last cycle - first dose date of first cycle)/28 + 1] for all 3 drugs. The actual duration of exposure for individual study drugs (days) will be calculated as follows:

1) If treatment is PEGPH20 and count of unique dates within last cycle is equal to 6 (cycle 1) or 3 (cycle 2 and beyond) , then use (min (first dose date of last cycle + 27 days, cutoff date, EOT date for discontinued subjects) – first dose date of first cycle+1).

  - If count of unique dates within last cycle is less than 6 (cycle 1) or 3 (cycle 2 and beyond) then use min (last dose date of last cycle, cutoff date) – first dose date of first cycle +1.

2) If treatment is NAB and count of unique dates within last cycle is equal to 3 then use min (first dose date of last cycle + 27 days , cutoff date, EOT date for discontinued subjects) – first dose date of first cycle +1.

  - If count of unique dates within last cycle is less than 3 then use min (last dose date of last cycle, cutoff date) – first dose date of first cycle +1.

3) If treatment is GEM, follow the same rule for NAB.

For the duration of exposure for drug regimen (PAG or AG), use the max (duration of exposure for individual drugs).

Duration of Exposure in days for individual study drugs at cycle 1 (C1):

1) If treatment is PEGPH20 and count of unique dates within C1 is equal to 6, then use min (first dose date of C1 + 27 days , cutoff date, EOT date for discontinued subjects) – first dose date of C1 +1.

- If count of unique dates within C1 is less than 6 then use min (last dose date of C1, cutoff date) – first dose date of C1 +1.

2) If treatment is NAB and count of unique dates within C1 is equal to 3 then use min (first dose date of C1 + 27 days , cutoff date, EOT date for discontinued subjects) – first dose date of C1 +1.

- If count of unique dates within C1 is less than 3 then use min (last dose date of C1, cutoff date) – first dose date of C1 +1.

3) If treatment is GEM, follow the same rule for NAB.

Summaries of dosing will include the number of non-zero dosing records over all cycles, actual dosing duration, cumulative dose, ADI, and RDI (see Section 5 for the definitions of ADI and RDI).

The following dose change variables will be calculated for each subject. Dose changes including dose delay and dose reduction will be summarized.

- Dose delay for a given cycle is defined as follows: Cycle length, defined as the number of days between the first-dose of the current cycle and that of the next cycle, will be calculated first. The planned cycle length is 28 days. A cycle is considered delayed if the preceding cycle length is greater than 35 days. Dose delay for each study drug will be determined similarly, except that the cycle length will be based on the first dose dates of each respective drug.
- Dose reduction is assigned if an administration of a weight- or BSA-adjusted dose during a cycle is smaller than that in the immediately preceding cycle by 15% or more. If subject is in cycle 1 then compare to the planned regimen starting dose for each study drug as shown in Table 7 above, respectively.
- The proportion of dose delays will be calculated as the number of cycles with dose delays divided by the total number of cycles given within each subject. Similarly, the proportion of dose reductions will also be calculated.

The number of subjects with PEGPH20 dosing changes (dose reduced or dose delayed) will be summarized for all cycles and in cycle 1 specifically.

Changes in NAB and GEM dosing will be summarized per treatment arm. Additionally, the total number of cycles with dose changed and the total number of subjects that have dose changes will be summarized for NAB and GEM. The proportion of doses delayed and reduced per subject will be summarized using the total number of cycles for each subject as the denominator for percentages.

A by-subject listing of compliance and study medication dosing based on the Safety population will be provided.

9.3.2 Prior and Concomitant Medications

Medications received concomitantly with study medication, categorized by medication preferred name according to World Health Organization Drug (WHODRUG) (v2012DEC01 DDE), will be summarized for the ITT population. The number and percentage of subjects using each preferred name will be displayed together with the number and percentage of subjects using any concomitant medication. Subjects taking more than 1 medication in the same preferred name will be counted once for the number of subjects taking that medication.

All medications taken during the screening period prior to receiving first dose of study treatment through 30 days after the last dose of study treatment including any herbal medications and vitamins are to be transcribed on the CRF.

Prior medications are those that the subject used prior to first dose date. Prior medications can be discontinued before first dosing or can be ongoing during treatment phase.

Concomitant medications are any treatments received by the subject concomitantly to any study treatment, from first dose date to the last dose date +30 days. A given medication can be classified both as a prior medication and as a concomitant medication.

Note that concomitant medications after last dose date +30 days are not transcribed on the CRF. For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as described in Section 9.7.

All prior and concomitant medication data and non-drug procedures will be presented in listings.

9.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

9.4.1 Demographics

Demographic and baseline characteristics will be summarized for the ITT population and Evaluable population. Descriptive statistics will be provided for age (<65 versus ≥65), sex (male versus female), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White/Caucasian, or other), Ethnicity (Hispanic or Non-Hispanic), KPS, baselines for weight (kg), height (m), and BSA (m^2). Additionally, baseline summaries will be presented for prior medication, general medical history, WBC > $11x10^9$ /L, Hemoglobin < 10 g/dL, and prior pancreatic cancer history including therapy, radiation, and surgery.

A by-subject listing of demographic and baseline characteristics will be provided.

9.4.2 Medical History

General medical history information will be summarized by category and conditions ongoing or resolved at study entry. Medical history conditions will be collected by eCRF. General medical history information will be summarized by category and preferred term.

A listing of medical history based on the ITT population will be provided by treatment and subject.

9.4.3 Pancreatic History

Pancreatic Cancer History will be summarized using the ITT population. The summary will include: location of primary tumor, sites of disease, biliary stents (yes or no).

A by-subject listing of medical history based on the ITT population will be provided, including the date of stage IV diagnosis, sites of metastasis, any previous pancreatic cancer (stage1-3), primary tumor location, and CA19-9.

9.4.4 Prior Pancreatic Cancer Therapy/Medication

Best response to prior pancreatic cancer therapy, surgery, and radiotherapy will be summarized.

Prior pancreatic cancer therapy, medication, and surgery will also be listed.

9.5 EFFICACY ANALYSES

All efficacy summaries will be presented for the ITT population. Primary efficacy analysis will also be presented for Evaluable Population. The Safety Population of Stage 2 will be used for analyses of efficacy data of Stage 2 of the study. The key analyses described below involving disease measurements will be based on central radiology results; exploratory analyses based on investigator assessment may be carried out.

9.5.1 Primary Variable

The primary efficacy endpoint is PFS. PFS is defined as the time from randomization until the first occurrence of disease progression, either by central radiologic determination or by clinical progression determined by the Investigator, or death during the treatment period from any cause. Surviving subjects without disease progression will be censored for the PFS analysis at the date of the last available post-baseline tumor assessment. Surviving subjects without any post-baseline disease assessment will be censored on Day 1.

Because the dosing interval between treatment cycles is 14 days, the treatment period will include 14 days after the last dose date. Thus, deaths occurring more than 14 days after the last dose date will not be considered as PFS events. Subjects with missing protocol scheduled tumor assessment(s) prior to radiologic disease progression will be considered as having disease progression on the date of the actual assessment of disease progression.

The survival distribution function (SDF) of PFS will be estimated using the Kaplan-Meier (KM) method (Cantor, 2001) and graphically displayed for each treatment group. Hence the estimates of the median, first and the third quartiles will be obtained and their 95% confidence interval (CI) will also be calculated (Brookmeyer and Crowley, 1982). The estimated proportion of subjects who are progression free at selected timepoints (e.g., 6 and 9 months, 1 year etc.) by treatment group (with 95% CIs) will also be calculated. Similar analyses will also be performed by tumor biopsy HA level (HA-high vs HA-low).

The primary PFS comparison of control (AG treatment group) with treatment (PAG treatment group) will be based on a stratified log-rank test at 2-sided $\alpha = 0.10$, where the stratum is the KPS category at screening defined earlier. The estimated hazard ratio (and 95% CI) for the overall treatment effect will be obtained using a stratified Cox regression model with the same stratification (Cox, 1972).

The PFS between the 2 groups based on HA level (HA-high or HA-low) of tested tumor biopsy will be evaluated using a Cox regression model repeated for each HA level.

9.5.2 Secondary Variables

OVERALL RESPONSE RATE

Best overall response will be determined based on the overall tumor response assessments performed by an independent central imaging vendor using RECIST 1.1 criteria (Appendix 4). The number and proportion of subjects who achieve CR, PR, SD, PD, not evaluable (NE), or Unknown as the best overall response will be summarized for each treatment group. Subjects with no available post-baseline tumor response assessments will have their best overall response set to 'Unknown'. Subjects with post-baseline scans who don't qualify for any of the CR, PR, SD or PD will be classified as NE.

The overall response rate calculated as a percentage is the number of subjects in the treatment group with an objective response rate (i.e., a best overall response of CR or PR) divided by the number of subjects in the population of interest multiplied by 100. The overall response rate will be calculated and its exact 95% confidence interval will be obtained (Clopper and Pearson, 1934).

Tumor response will be presented in a subject listing sorted by treatment group. Information included in the listing will be best tumor response, overall survival, response onset date, PD date, progression free survival duration, death date, and DOR. Lesion Assessments will also be presented in a subject listing and includes: the assessment date, lesion type, lesion site, method of assessment, diameter of each target lesion and sum of diameters (SOD) of target lesions, and the change in each target lesion diameter and SOD from baseline.

The ORR will be compared between the 2 treatment groups using the Cochran-Mantel-Haenszel test (Wittes and Wallenstein, 1993) stratified by the KPS category at screening defined earlier. In addition, for

each HA subgroup (HA-high and HA-low) the ORR data will be summarized and compared between the 2 treatment groups analogously.

OVERALL SURVIVAL

Overall survival data will be analyzed analogous to PFS data.

9.5.3 Exploratory Variables

DURATION OF RESPONSE

KM method will be used to estimate the survival distribution function of duration of response (DOR). Hence the median, first and third quartiles will be estimated and their 95% CIs will also be calculated by treatment group using the same techniques described under the analysis of PFS. DOR analysis will be performed using only the subjects with an objective response (i.e., subjects with a best response of CR or PR). Similar analysis will be done for each HA subgroup (HA high vs HA low).

DISEASE CONTROL RATE

Disease Control Rate will be calculated for each treatment group for the population of interest and analyzed analogous to ORR.

CA19-9

Baseline CA19-9, descriptive statistics, changes from baseline, and decrease categories (<20%, >=20%, >=50%, >=70%) for each visit for the PAG and AG treatment groups will be summarized. Values of CA19-9 for each visit will be listed by subject.

9.6 SAFETY ANALYSES

The Safety Population will be used for overall safety analyses. The Safety Population of Stage 2, which is the analysis population for the primary safety endpoint, will be used to analyze the safety data of subjects who are randomized in Stage 2 of the study.

9.6.1 Analysis of Primary Safety Endpoint

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

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

Null hypothesis: $P \leq 12\%$

Alternative hypothesis: $P > 12\%$

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

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

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

- Final analysis: enoxaparin dose: 1 mg/kg/day (58 PAG subjects).

The DMC may recommend terminating the study when any of the four safety analyses cross the stopping boundaries as described in Table 8:

Table 8: Stopping Boundaries for Subjects in the PAG Arm of Study 202, Stage 2

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

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

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

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

In addition to the primary safety endpoint analysis, the incidence rate of thromboembolic events will also be summarized by treatment group for the Safety Population. Additional thromboembolic summaries will be conducted for two Stage 2 population subgroups characterized by the subjects' enrolment timepoint relative to the protocol version and their initial Enoxaparin dosage (refer to Section 6 for more details).

9.6.2 Adverse Events

All summaries of adverse events (AEs), unless otherwise stated, will include only treatment-emergent events. A summary of AEs, including the number and percentage of subjects reporting at least 1 AE, a National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE; v4.03) Grade 3 or higher AE, Adverse Events Leading to Discontinuation of Study Medication, a serious adverse event (SAE), study medication related serious adverse events, and AEs leading to death (defined as CTCAE Grade 5 or outcome is "fatal") will be presented. A breakdown of the number and percentage of subjects reporting each AE, categorized by System Organ Class (SOC) and preferred term coded according to the Medical Dictionary for Regulatory Activities (MedDRA, v15.1), will be presented. AEs will be counted by subject, not by event, and subjects will be counted only once within each SOC or preferred term. Summaries will be repeated for SAEs and maximum CTCAE Grade ≥3 AEs. Study day is calculated as date of event (death, SAE, etc.) – first dose date +1. Days since last dose are calculated as event date - last dose date +1.

Table summaries of AE's related to PEGPH20, NAB, and GEM will be presented. Relationship to study medication will be determined as any category other than not related, unlikely related or not applicable. If "Yes, Related" or "Probably Related" or "Possibly Related", the relationship is "Yes"; if "Unlikely

Related" or "Not Related", the relationship is "No". A similar summary will be generated for treatment-related AEs, SAEs, and maximum CTCAE Grade ≥3 AEs.

Adverse events coded as CTCAE Grade 5 or with an outcome of "Fatal" will be considered AEs leading to death and will be summarized separately in addition to overall grading.

A summary of AEs reported, categorized by NCI CTCAE v4.03 grades, will also be provided. Subjects with multiple events within a particular SOC or preferred term will be counted under the category of their most severe AE within that SOC or preferred term. This will be repeated for treatment-related AEs as defined above.

Additionally, treatment-related SAEs will be summarized.

A further tabulation presenting the preferred terms for the AEs occurring in ≥5% of subjects in the total column and in the PAG group will also be presented in descending order of frequency. This summary will be repeated for study-drug related AEs.

All summarized AEs will be listed by subject.

9.6.3 Deaths, Serious Adverse Events, and Adverse Events Leading to Study Discontinuation

A listing of subjects who died will be presented. Subject deaths will be determined from end of study data (where reason for discontinuation is death), AE data (where CTCAE grade is 5 or outcome is "fatal") , follow-up pages (where follow-up status is listed as death), and from the death report page. The number of days between first dose and death will be calculated as (date of death – first dose date + 1). The number of days between last dose and death will be calculated as (date of death – last dose date + 1).

Subjects who experienced an SAE will be listed. Additionally, a listing of all deaths on study, including the treatment phase and follow-up will be generated.

A summary of AEs leading to discontinuation of study medication will be provided by SOC and preferred term. An AE leading to discontinuation is defined as any AE with an action code of "Study Drug Discontinued". The date of discontinuation will be defined as the date on the treatment discontinuation eCRF page. Additionally, a by-subject listing of AEs leading to discontinuation will be provided.

9.6.4 Laboratory Data

Laboratory data (including values, units and normal ranges) will be entered at a central vendor based on lab reports obtained from the study sites. Only data from the Central Lab will be summarized and local laboratory data will not be considered. Central lab data are reported in SI units. A list of the SI units used to present laboratory data is provided in Appendix 2 of this document.

In general, laboratory data presented by visit will be presented through Cycle 6 Day 1 (end of Cycle 5) and the treatment discontinuation visit. A summary of Maximum Post-baseline Grades and a shift summary from baseline to worst post baseline by maximum CTCAE grades will also be presented.

HEMATOLOGY

The following hematology tests will be summarized in the following groups:

- White blood cell (WBC) parameters: Total WBC count, basophils, eosinophils, lymphocytes, monocytes, neutrophils and granulocytes.
- Red blood cell (RBC) parameters: Hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, and RBC count.

- Other parameters: Platelets count.

Descriptive statistics will be provided for each test result and for change from baseline by scheduled visit. Multiple measurements taken during the visit for a subject will be represented by the most severe value for each hematology test. The most severe value will be determined first by the value closest to the upper or lower limit of the normal limits (dependent on which direction is considered severe) if the value is within the normal limits. If the value is outside the normal limits, the value furthest from the upper or lower limit will be selected (dependent on which direction is considered severe). In the event that this algorithm does not allow for determining the most severe (i.e., a tie) the first chronological value will be selected. Low values are considered the most severe for all hematology analytes. Subjects who develop ≥ Grade 3 toxicity will be listed.

CHEMISTRY

The following chemistry tests will be summarized in the following groups:

- Hepatobiliary parameters: Alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, total bilirubin, and direct bilirubin.
- Renal function tests: Blood urea nitrogen and creatinine.
- General serum chemistry: Albumin, chloride, glucose, sodium, potassium, bicarbonate, corrected calcium, and magnesium.

Where corrected calcium is derived with the following formula:
Corrected calcium (mmol/L) = (0.02 * (40 (g/L) – normal albumin (g/L))) + serum calcium (mmol/L).

Descriptive statistics will be provided for each test result and for change from baseline by visit. Multiple measurements taken during the visit for a subject will be represented by the most severe value as noted in the hematology section. For all chemistry analytes, the most severe value is the highest value, with the exception of LDH, albumin, chloride, and bicarbonate where the lowest value is the most severe. The most severe could be in either direction for glucose, potassium, sodium, calcium and magnesium. For these analytes, if within the normal limits, the value closest to the normal limit (either direction) will be selected. If outside the normal limits, the value most distant from the normal limit (either direction) will be used. Subjects who develop a ≥ Grade 3 toxicity will be listed.

COAGULATION

The coagulation tests prothrombin time, partial thromboplastin time, International normalized ratio (INR), and anti-Xa are reported by the clinical site laboratory at screening only (per protocol) and will be listed.

URINALYSIS

Subject urinalysis test results will be listed including the parameters pH, glucose, blood, ketones, protein, nitrite, specific gravity, and leukocytes. The listing will include the sample date and time and will report the normal range of each parameter.

CTCAE CODING OF LABORATORY DATA

Where laboratory values are categorized into NCI CTCAE v4.03 grades, the categories are defined according to the criteria available on the following website:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Note that grades are applied based only on the numeric value of the parameter assessed; clinical signs and symptoms are not considered. For example, Grade 4 hyperglycemia will be assigned based solely on the value of the glucose measurement and acidosis will not be considered. Where categories are only distinguished by clinical signs or symptoms, the lowest of the possible grades will be assigned.

NCI CTCAE v4.03 grades will be applied for the following lab parameters (given in Appendix 3):

- Hematology: hemoglobin (anemia), total WBC (leucopenia), lymphocytes (lymphopenia), neutrophils (neutropenia) and platelets (thrombocytopenia).
- Chemistry: albumin (hypoalbuminemia), alkaline phosphatase, ALT, AST, bilirubin (hyperbilirubinemia), corrected calcium (hypocalcemia, hypercalcemia), creatinine, glucose (hyperglycemia, hypoglycemia), magnesium (hypermagnesemia, hypomagnesemia), potassium (hyperkalemia, hypokalemia), and sodium (hyponatremia, hypernatremia).

A summary of maximum severity observed on-study treatment for all parameters noted above will be generated for the coded hematology and chemistry parameters. Subjects will only be included once, in the maximum severity, for each laboratory parameter. Additionally, a shift summary of baseline to maximum severity on-study treatment will also be produced. Subjects with at least 1 on-study treatment measurement for each laboratory parameter will be included, regardless of whether or not a baseline assessment is present (baseline will be included as a missing category). Thus, percentages for each parameter will be based on the total number of subjects with an on-study treatment measurement for the parameter of interest.

Laboratory measurements that are within their institutional limits of normal and are not graded as 1-4, per the CTCAE, will be summarized as "Grade 0," which is defined as normal.

9.6.5 Vital Signs

The following vital signs will be summarized: pulse rate, blood pressure, respiration rate, temperature, and weight. Vital signs and change from baseline will be summarized in 2 ways. First, all vital signs and changes from baseline through Cycle 6 Day 1 and the end of treatment visit will be summarized. In these tables, baseline will be the Cycle 1 Day 1 measurement for all comparisons, if available, otherwise the most recently measured values prior to Cycle 1 Day 1 within 14 days will be considered baseline. An out-of-range summary of vital sign results will be presented including all post-baseline measurements. Vital signs results will be provided in data listings by subject.

9.6.6 Physical Examinations, ECGs, and Other Observations Related to Safety

PHYSICAL EXAMINATIONS

The occurrence of any normal or abnormal (not clinically significant or clinically significant) findings will be listed for the following body systems: general appearance, head, ears, eyes, nose and throat, cardiovascular system, respiratory system/chest, gastrointestinal system, musculoskeletal system, and central peripheral nervous system. Additionally, any condition descriptions associated with the event will be provided in subject data listings.

Physical examination data collected at scheduled and unscheduled visits will not be summarized, but will be included in data listings.

CARDIAC STUDIES

Corrected QT interval using the Fridericia's formula ($QTcF = QT/(RR)^{1/3}$) will be derived from the ECG page data. Twelve-lead ECGs with assessment of QTcF intervals will be obtained in triplicates during study visits as specified in the Schedule of Assessments. Change from baseline in ECG results will be summarized by treatment arm. Baseline QTcF will be defined as the average of the 3 tracings taken at Cycle 1 Day 1, pre-dose. The average of the 3 tracings at baseline and all visits through Cycle 6 Day 1 and the end of treatment visit will be summarized. This will include a summary of the maximum values observed while the subject was on treatment. Additionally, the following categorizations will be

summarized: Absolute QTC interval ≤ 450 milliseconds (msec), >450-480 msec, >480-500 msec and >500 msec; QTc change from baseline ≤30 msec, >30-60 msec and >60 msec. Subjects who experienced a QTc result with a grade ≥ 3 will be presented in a listing.

Shift tables by maximum CTCAE grade (frequency and %, see Appendix 3 for coding) for QTcF intervals will be provided inclusively for all subjects in the Safety population by treatment arm. These tables will compare the baseline value relative to its maximum post-baseline NCI-CTCAE grade.

A table summarizing post-baseline abnormal ECG results will also be presented.

All ECG data will be provided in data listings.

KARNOFSKY PERFORMANCE STATUS

Karnofsky performance status will be recorded at Screening and during study visits as specified in the Schedule of Assessments. Baseline KPS will be assessed at Cycle1 Day 1, pre-dose.

All KPS data will be provided in data listing.

SURVIVAL FOLLOW-UP

The duration of survival follow-up is defined as time from randomization date to the date of death or the date subject last known to be alive.

If a subject dies, the duration in days will be calculated as:

date of death –randomization date + 1, with censor variable =0 (event for follow up).

If a subject is alive, the duration will be calculated as:

date subject last known to be alive –randomization date + 1 , with censor variable=1 (censored for follow up).

9.7 METHODS FOR HANDLING DROPOUTS AND MISSING DATA

Time to event parameters will be censored if subjects withdraw, drop out, or are lost to follow-up before documentation of the events (PD/death).

All available efficacy and safety data will be included in data listings and tabulations. In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified.

Missing/Partial Dates in Adverse Events/Concomitant Therapies/ Subsequent Therapies

Every effort will be made to avoid missing/partial dates in on-study data.

Adverse event stop dates that are completely or partially missing will be imputed as follows:

- If the stop date has month and year but day is missing, the last day of the month will be used to impute the missing day.
- If the stop date has year, but day and month are missing, then 31DEC will be used to impute the missing day and month.

After the imputation, the imputed dates will be compared against the date of death, if available. If the date is later than the date of death, the date of death will be used as the imputed date instead.

Adverse event start dates that are completely or partially missing will be imputed as follows:

- If the start date has month and year but day is missing, the first day of the month will be used to impute the missing day.
    - If this date is earlier than the first dose date, then the first dose date will be used instead.

- If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

- If the start date has year, but day and month are missing, then 15 JUN will be used to impute the missing day and month.
  - If this date is earlier than the first dose date and the year is the same as the year of the first dose date, then the first dose date will be used instead.
  - If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

If the start date of an event is completely missing, then it will be imputed with the first dose date.

Concomitant therapies with start dates that are completely or partially missing will be analyzed as follows:

- If the start date has month and year but day is missing, the therapy will be included in the summary table if the month and year of the start date of the event are:
  - On or after the month and year of the date of the first dose of study drug

and

  - On or before the month and year of the date of the last dose of study drug plus 30 days.

- If the start date has year, but day and month are missing, the therapy will be included in the summary table if the year of the start date of the event is:
  - On or after the year of the date of the first dose of study drug

and

  - On or before the year of the date of the last dose of study drug plus 30 days.

If the start date of a therapy is completely missing, then the therapy will be included in the summary table.

Subsequent therapies with start dates that are completely or partially missing will be analyzed as follows:

- When month and year are present and the day of the month is missing,
  - If the onset month and year are the same as the month and year of last dose with study drug, the day of last dose + 1 will be used to impute the missing day.
  - If the onset month and year are not the same as the month and year of last dose with study drug, the first day of the month will be used to impute the missing day.

- When only the year is present,
  - If the onset year is the same as the year of last dose with study medication, the date of last dose + 1 will be to impute the partially missing date.
  - If the onset year is not same as the year of last dose with study medication, the first day of the year will be used to impute the partially missing date.

- If no components of the onset date are present the date of last dose + 1 will be used to impute the missing date.

Handling of missing relationship to study treatment of AEs

If an AE relationship is missing, it will not be imputed.

Handling of missing grades of AEs

If the grade or intensity of an AE is missing, no imputation will be performed.

10. VALIDATION

PRA Health Sciences seeks to ensure the quality of the results provided for the study in the form of TFLs, SDTM and ADaM datasets used in their creation, through the following processes:

- Derived datasets are independently reprogrammed by a second programmer. The separate datasets produced by the 2 programmers must match 100%. Detailed specifications for the derived datasets are documented in the study Data Mapping Tool provided to the client at study conclusion.
- Tables are independently reprogrammed by a second programmer for numeric results.
- Figures are checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.
- Listings are double programmed and checked for consistency against corresponding tables, figures, and derived datasets.

The entire set of TFLs is checked for completeness and consistency prior to its delivery to the client by the lead clinical programmer, the lead statistician, and a senior level statistician, or above, who is not a member of the project team.

The PRA Health Sciences validation process is repeated any time TFLs are redelivered using different data. Execution of this validation process is documented through the study Table of Programs that is provided to the client at study conclusion.

11. REFERENCES

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APPENDIX 1 GLOSSARY OF ABBREVIATIONS

ADI	Actual dose intensity
AE	Adverse event
AG	Nab-Paclitaxel, Gemcitabine
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
BSA	Body surface area
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DOR	Duration of response
ECG	Electrocardiogram
eCRF	Electronic case report form
EE	Efficacy Evaluable
GEM	Gemcitabine
HA	Hyaluronan
KM	Kaplan-Meier
KPS	Karnofsky Performance Status
MedDRA	Medical Dictionary for Regulatory Activities
NAB	Nab-Paclitaxel
Nab	Albumin bound form
NCI	National Cancer Institute
NE	Not evaluable
ORR	Overall response rate
OS	Overall survival
PAG	PEGPH20, Nab-Paclitaxel, Gemcitabine
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
QTcF	QT intervals corrected for heart rate, using Fridericia's criteria
RBC	Red blood cell
RDI	Relative Dose Intensity
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SI	Standard international
SOD	Sum of diameter
SOC	System organ class
TE	Thromboembolic
TFL	Tables, figures and listings
WBC	White blood cell
WHODRUG	World Health Organization Drug

APPENDIX 2 LABORATORY STANDARD UNITS

Laboratory Test	SI Unit
Albumin	g/L
Alkaline Phosphatase	U/L
Absolute neutrophil count	10^9/L
Basophils	10^9/L
Bicarbonate	mmol/L
Total Bilirubin	µmol/L
Blood Urea Nitrogen	mmol/L
Calcium	mmol/L
Chloride	mmol/L
Creatinine	µmol/L
Eosinophils	10^9/L
Glucose	mmol/L
Granulocytes	10^9/L
Hematocrit	frac of 1
Hemoglobin	g/L
INR	1
Lymphocytes	10^9/L
Magnesium	mmol/L
Mean Corpuscular Hemoglobin	pg
Mean Corpuscular Volume	fL
Monocytes	10^9/L
Platelets	10^9/L
Potassium	mmol/L
Total Protein	g/L
Prothrombin Time	s
Partial Thromboplastin Time	s
Red Blood Cells	10^{12}/L
Aspartate Transaminase	U/L
Alanine Transaminase	U/L
Sodium	mmol/L
White Blood Cells	10^9/L

APPENDIX 3 CTCAE V4.03 GRADING FOR LABORATORY VALUES AND QTCF

CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 × 10^9/L	<3000 - 2000/mm^3; <3.0 - 2.0 × 10^9/L	<2000 - 1000/mm^3; <2.0 - 1.0 × 10^9 /L	<1000/mm^3; <1.0 × 10^9/L
Blood and lymphatic system disorders	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Investigations	Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x10^9 /L	<800 - 500/mm^3; <0.8 - 0.5 × 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 × 10^9 /L	<200/mm^3; <0.2 × 10^9 /L
Investigations	Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 × 10^9/L	<1500 - 1000/mm^3; <1.5 - 1.0 × 10^9/L	<1000 - 500/mm^3; <1.0 - 0.5 × 10^9/L	<500/mm^3; <0.5 × 10^9/L
Investigations	Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 × 10^9/L	<75,000 - 50,000/mm^3; <75.0 - 50.0 ×10^9/L	<50,000 - 25,000/mm^3; <50.0 - 25.0 ×10^9/L	<25,000/mm^3; <25.0 ×10^9/L
Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated
Investigations	Alkaline phosphatase increased	>ULN - 2.5 × ULN	>2.5 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Investigations	Alanine aminotransferase increased	>ULN - 3.0 × ULN	>3.0 – 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Investigations	Aspartate aminotransferase increased	>ULN - 3.0 × ULN	>3.0 – 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Investigations	Blood bilirubin increased	>ULN - 1.5 × ULN	>1.5 - 3.0 × ULN	>3.0 - 10.0 × ULN	>10.0 × ULN
Metabolism and nutrition disorders	Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences

CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	Creatinine increased	>1 - 1.5 × baseline; >ULN - 1.5 × ULN	>1.5 - 3.0 × baseline; >1.5 - 3.0 × ULN	>3.0 baseline; >3.0 - 6.0 × ULN	>6.0 × ULN
Metabolism and nutrition disorders	Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures
Metabolism and nutrition disorders	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences
Electrocardiogram QT corrected interval prolonged		QTcF > 450 to ≤ 480 ms	QTcF > 480 to ≤ 500 ms	QTcF> 500 ms	

Note: Laboratory measurements that are within their institutional limits of normal and are not graded as 1-4, per the CTCAE, will be summarized as “Grade 0”, which is defined as normal.

APPENDIX 4 RESPONSE EVALUATION CRITERIA (RECIST V1.1)

Target Lesion Response Evaluation:

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

Non-Target Lesion Response Evaluation:

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

Overall Response Evaluation:

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

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

APPENDIX 5 DATA BLINDING AND DOCUMENTATION OF AGGREGATE DATA DISSEMINATION

Purpose

The purpose of this work instruction is to define the process for managing data handling and dissemination of clinical data during the conduct of Study HALO-109-202. In addition, this work instruction describes efforts taken to restrict sponsor access to individual/aggregated data in order to maintain integrity of the study to support regulatory submissions while still allowing the sponsor sufficient access to defined data to promote subject safety and support study management.

Blinding of Clinical Database

The study team will conduct programming activities using data from the clinical database altered to hide treatment arm designation. Based on the agreement dated on 4May2015 by Halozyme Inc. and PRA, PRA Biostatistics, programming and data management (DM) functions will no longer be blinded to aggregate study results by treatment arm. However, Clinical Operations and Project Management functions will remain blinded. This agreement supersedes Appendix B of the DMC Charter. Access to the protected unblinded folders will be controlled by the PRA project manager, who will authorize PRA information technology to grant access to appropriate people on the reporting team.

Prior to 04May2015, the clinical programmer was unblinded and prepared macros to extract the data in both a blinded and unblinded form. The unblinded (direct) database extract was stored in the unblinded restricted access folder system. The blinded data extract was available to the study team in PRAs usual folder structure. In addition, the following fields were removed from the clinical database extract to prevent the study team from knowing the treatment arm of study subjects:
Adverse Events – Action Taken with PEGPH20 – AEACN1
Adverse Events – Is this event related to PEGPH20 – AEREL1
Randomization – Treatment Arm – RANDARM – Screening
Exposure – PEGPH20 whole form

- Cycle 1: Days 1, 4, 8, 11, 15, 18
- All other Cycles: Days 1, 8, 15

Exposure – nab-Paclitaxel whole form

- Cycle 1: Days 1, 2

Exposure – Gemcitabine whole form

- Cycle 1: Days 1, 2

Add Unscheduled Forms – Exposure – PEGPH20 – ADDEXP
Presence of PK pages

- Run-In Phase
    - Cycle 1: Days 1, 2, 4, 8, 11, 15, 18
    - Cycle 2 and over: Day 8
- Phase 2
    - Cycle 1: Days 1, 2, 15

- Cycle 2 and over: Day 8

Central Lab Pages if Panel Name = Immunogenicity

- All cycles day 1 and End of Treatment

Thromboembolic Risk Factor Assessment – Was PEGPH20 re-started?
Thromboembolic Risk Factor Assessment –Date of PEGPH20 re-start?
After 04May2015, the blinded data extract is no longer required.

General Data handling
For the Phase 2 portion of the study, in general, safety oversight will be managed as follows:
Individual Patient Data
Access to treatment codes will be provided to the team as required to complete study- related activities, e.g., CRAs for monitoring purposes, IVRS, Safety personnel for possessing, monitoring and reporting of safety data.

Aggregate Safety Data

Prior to 04May2015, access to aggregate safety data by treatment arm was restricted to the safety officer, medical monitor, Data Monitoring Committee (DMC), and Independent Reporting Group (IRG) including the independent reporting statistician, [redacted] from Halozyme had access to the unblinded monthly and quarterly DMC safety reports including SAEs and AEs of special interest. Additional unblinded personnel were documented in the unblinded interim analysis plan (UIAP). Any review of unblinded aggregate safety data was documented in an unblinded interim analysis plan, which was filed in the eTMF. After 04May2015, aggregate safety data by treatment arm will not be accessible to Clinical Operations and Project Management personnel.

Aggregate Efficacy Data
Prior to 04May2015, access to aggregate efficacy data by treatment arm was restricted to the DMC and the ISG, including the independent reporting statistician. Any review of unblinded aggregate efficacy data would be documented in an unblinded interim analysis plan, which would be filed in eTMF.
After 04May2015, aggregate efficacy data by treatment arm will not be accessible to Clinical Operations and Project Management personnel.

After 21Sep2015, aggregate efficacy data by treatment arm will not be accessible to Halozyme Biostatistics department personnel. Between 04May2015 and 21Sep2015, this information may have been accessible to Halozyme Biostatistics through data transfers.

For Stage 1 portion of the study

Efficacy analysis was conducted on Stage 1 data of the study by the sponsor and Ventana Medical Systems Inc. in order to develop the HA algorithm and determine the HA cut-point for the Phase 3 confirmatory study, HALO-109-301 study.

For the Stage 2 portion of the study:

Stage 2 efficacy data will be used to validate the HA cut-point derived from Stage 1 data. The following data will be blinded to the sponsor until the database is locked and the final analysis is completed:

- The tumor assessment by central readers, which will be used to define ORR and PFS efficacy endpoint.
- HA scores of Stage 2 subjects, which will be used to define HA-high and HA-low subgroups.

Additional Data

Any dissemination of aggregate data by treatment arm beyond the persons outlined above could compromise the confirmatory status of the study and have impact on its suitability to support marketing approval. In the event that access to additional aggregate safety data is determined to be necessary, the dissemination of this data will be clearly documented in a note to file in the study Trial Master File.

- An unplanned analysis of aggregate safety data was performed by Halozyme and documented in a note to file on 02May2014.
- Aggregate unblinded data was reviewed as outlined in the Interim Unblinding Analysis Plan (28Oct2014).
- All efficacy data for Stage 1 only with data cut on 05Dec2014 were reviewed by Halozyme.
- Documentation of the accidental unblinding that occurred in April2015 will be filed via NTF.
- A pre-freeze dry run was performed on 17Aug2015 (with some additional re-shipments of outputs on the same data) which was based on a database snapshot taken 16Jul2015. These results contained aggregate data by treatment arm for both safety and efficacy, and for both Stage 1 and Stage 2.
- On September 26, 2016, the 5 central imaging (Imaging Endpoints) tumor response related source datasets TL,TL2, NTL, NTL2, and STAT based on September 24, 2016 data extract were transferred to Halozyme programming and statistics with the subject identifiers masked, but were done in such a way that all records from an individual subject are linked across all five datasets so that Halozyme can perform consistency checks as part of the data review process before database lock. All available Stage 2 data were included in this data transfer.
- PRA will make a raw data transfer that include efficacy results by central imaging and exposure data for all stage 2 patients on 16DEC2016. At the same time, or as soon as possible thereafter, PRA will also include the Ventana CAP/CLIA HA data. PRA will deliver unblinded top-line TFL's that include aggregate primary efficacy results by HA subgroups on 04JAN2017.