Clinical Study Protocol Amendment

Test Drug:	E7389
Protocol Number:	E7389-M000-219
Protocol Title:	A Randomized, Open-label, Multicenter, Phase 1b/2 Study of Eribulin Mesylate in Combination with PEGylated Recombinant Human Hyaluronidase (PEGPH20) versus Eribulin Mesylate Alone in Subjects with Human Epidermal Growth Factor Receptor 2 (HER2)-Negative, High-Hyaluronan (HA) Metastatic Breast Cancer (MBC)
Date of Original Protocol:	25 April 2016
Date of Protocol Amendment 01:	27 Oct 2016

ORIGINAL TEXT			**AMENDED TEXT**		
SYNOPSIS			**SYNOPSIS**		
Approval Date:	V1.0	25 Apr 2016 (Original Protocol)	Approval Date:	**V2.0**	**27 Oct 2016 (Amendment 01)**
Study Period and Phase of Development Duration Overall: Approximately 30 months Duration by Subject: Estimated median treatment duration is 8 months, although subjects may remain on study treatment as long as the subject demonstrates clinical benefit. Study Interval: The study is estimated to begin in May 2016 and end in or before October 2018 (includes enrollment of approximately 18 months).			**Study Period and Phase of Development** Duration Overall: Approximately ~~30~~ **36** months Duration by Subject: Estimated median treatment duration is 8 months, although subjects may remain on study treatment as long as the subject demonstrates clinical benefit. Study Interval: The study is estimated to begin in May 2016 and end in or before **April 2019** (includes enrollment of approximately **24** months). ~~Study Interval: The study is estimated to begin in May 2016 and end in or before October 2018 (includes enrollment of approximately 18 months).~~		
Reason(s) for the Amendment: *Administrative*					
ORIGINAL TEXT			**AMENDED TEXT**		
SYNOPSIS AND SECTION 8.1			**SYNOPSIS AND SECTION 8.1**		
Objectives **Primary Objectives**			**Objectives** **Primary Objectives**		
• For the Phase 1b part – to determine safety tolerability and recommended Phase 2 dose (RP2D) of eribulin mesylate in combination with PEGPH20 in subjects with HER2-negative MBC previously treated with 0 to 1 line of systemic anticancer therapy in the metastatic setting. • For the Phase 2 part – to evaluate objective			• For the Phase 1b part – to determine safety tolerability and recommended Phase 2 dose (RP2D) of eribulin mesylate in combination with PEGPH20 in subjects with HER2-negative MBC previously treated with ~~0 to 1 line~~ **up to two lines** of systemic anticancer therapy in the metastatic setting. • For the Phase 2 part – to evaluate objective		

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response rate (ORR) of eribulin mesylate in combination with PEGPH20 in subjects with HER2-negative, HA-high, MBC previously treated with 0 to 1 line of systemic anticancer therapy in the metastatic setting.	response rate (ORR) of eribulin mesylate in combination with PEGPH20 in subjects with HER2-negative, HA-high, MBC previously treated with ~~0 to 1 line~~ **up to two lines** of systemic anticancer therapy in the metastatic setting.
SYNOPSIS AND SECTION 8.3	**SYNOPSIS AND SECTION 8.3**
Exploratory Objectives • To identify and explore tumor and blood markers that correlate with clinical outcomes, including efficacy	Exploratory Objectives • To identify and explore tumor and blood markers **(e.g., Plasma HA levels)** that correlate with clinical outcomes, including efficacy

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Reason(s) for the Amendment:

Study design modified to include patients in later lines based on Investigator feedback and allow for the combination to be used in a broader patient population.

Exploratory objectives updated due to addition of HA plasma sample collection

ORIGINAL TEXT	AMENDED TEXT
SYNOPSIS and Section 9.1	***SYNOPSIS and Section 9.1***
Study Design	**Study Design**
This is a randomized, open-label, multicenter, Phase 1b/2 study of eribulin mesylate in combination with PEGPH20 versus eribulin mesylate alone in subjects with HER2-negative, HA-high, MBC previously treated with 0 to 1 line of systemic anticancer therapy (cytotoxic or targeted anticancer agents) in the metastatic setting.	This is a randomized, open-label, multicenter, Phase 1b/2 study of eribulin mesylate in combination with PEGPH20 versus eribulin mesylate alone in subjects with HER2-negative, HA-high, MBC previously treated with ~~0 to 1 line~~ **up to 2 lines** of systemic anticancer therapy (cytotoxic **drugs** or targeted anticancer agents**)**in the metastatic setting. **CDK4/6 inhibitors and mTOR inhibitors will not be considered as prior lines of therapy. Any single agents or combination of scheduled pre-planned treatments (given concomitantly, sequentially, or both) is considered as one regimen. Hormonal therapy and bone metastases treatment (eg, bisphosphonates, denosumab, etc) are not considered forms of systemic anticancer therapy.**
The Phase 1b part will have dose-limiting toxicity (DLT) assessed in the first cycle…..	**Phase 1b occurs in two parts:** **Part 1: Conduct run-in safety cohorts (dose levels 1, 0, and -1, as necessary) of 6 subjects each, until RP2D is determined as follows:** • The Phase 1b part **1** will have dose-limiting toxicity (DLT) assessed in the first cycle…..
Otherwise, alternative doses will be explored prior to the start of Phase 2.	…Otherwise, alternative doses will be explored prior to the start of Phase 2. **Part 2: Upon determination of the RP2D, begin Phase 1b "Expansion Part" by enrolling 12 additional subjects (using Phase 1b criteria, ie, subjects previously treated with up to 2 lines of systemic anticancer therapy) at the RP2D. This will result in a total of 18 subjects at RP2D for further safety analysis.** **Following completion of one treatment cycle by the Expansion Part subjects, a safety evaluation of all Phase 1b subjects, focusing on incidence of TE events, will be conducted prior to proceeding with the Phase 2 part of the study.** **If ≤ 1 out of 18 subjects experience a TE event,**

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	the upper limit of the 1-sided 80% exact CI for the true TE rate will not be greater than 15.7%. If ≤ 2 out of 18 subjects experience a TE event, the upper limit of the 1-sided 80% exact CI for the true TE rate will not be greater than 22.3%. If more than 2 TE events occurs in 18 subjects in Phase 1b, then the sponsor in collaboration with Halozyme will decide on further required changes to the study conduct.
Pharmacokinetic (PK) assessments of eribulin mesylate and PEGPH20 will be performed in all subjects in the Phase 1b part of the study. Only subjects receiving combination treatment with PEGPH20 and eribulin mesylate (Arm A) in the Phase 2 part will undergo sparse PK sampling for population pharmacokinetic /pharmacodynamic (PK/PD) analysis, where feasible.	Pharmacokinetic (PK) assessments of eribulin mesylate and PEGPH20 will be performed ~~in all subjects in the Phase 1b part of the study~~ **for all 12 subjects in the Phase 1b Expansion Part**. Only subjects receiving combination treatment with PEGPH20 and eribulin mesylate (Arm A) in the Phase 2 part will undergo sparse PK sampling for population pharmacokinetic/pharmacodynamic (PK/PD) analysis, where feasible.
Reason(s) for the Amendment: *Study design modified to include patients in later lines based on Investigator feedback and allow for the combination to be used in a broader patient population.* *Added additional details to further clarify definition of systemic anticancer therapy.* *Rationale of adding the Phase 1b expansion part is based on safety considerations (discussed and required by Eisai Sr Management and GSO).* *PK being done only in expansion part patients since all these patients will be treated at RP2D and PK sampling data from 12 patients is adequate.*	

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ORIGINAL TEXT	AMENDED TEXT
SYNOPSIS and ***Section 9.3.1***	*SYNOPSIS and* ***Section 9.3.1***
Inclusion Criteria 3. Human epidermal growth factor receptor 2-negative (defined as immunohistochemistry [IHC] <2+ or fluorescence in situ hybridization [FISH] negative) breast cancer previously treated with 0 to 1 line of systemic anticancer therapy (cytotoxic or targeted anticancer agents) in the metastatic setting. Hormonal therapy and bone metastases treatment (eg, bisphosphonates, denosumab, etc) are not considered forms of systemic anticancer therapy.	**Inclusion Criteria** 3. ~~Human epidermal growth factor receptor 2-negative (defined as immunohistochemistry [IHC] <2+ or fluorescence in situ hybridization [FISH] negative) breast cancer previously treated with 0 to 1 line of systemic anticancer therapy (cytotoxic or targeted anticancer agents) in the metastatic setting. Hormonal therapy and bone metastases treatment (eg, bisphosphonates, denosumab, etc) are not considered forms of systemic anticancer therapy.~~ **Metastatic breast cancer meeting the following criteria:** **a. Human epidermal growth factor receptor 2-negative, defined as immunohistochemistry (IHC) <2+ or fluorescence in situ hybridization (FISH) negative.** b. **Previously treated with up to two lines of systemic anticancer therapy (cytotoxic drugs or targeted anticancer agents) in the metastatic setting. CDK4/6 inhibitors and mTOR inhibitors will not be considered as prior lines of therapy. Any single agents or combination of scheduled pre-planned treatments (given concomitantly, sequentially, or both) is considered as one regimen. Hormonal therapy and bone metastases treatment (eg, bisphosphonates, denosumab, etc) are not considered forms of systemic anticancer therapy**.
4. Archived tissue sample or new biopsy sample: Metastatic breast cancer tissue with HA-high levels based on available tumor tissue in formaldehyde fixed-paraffin embedded (FFPE) block or minimum of 5 (10 preferred) unstained core biopsy slides that meet specific tissue sample requirements. Fine needle aspirates (FNA) or brushing biopsies will not be acceptable.	4. Archived tissue sample or new biopsy sample: Metastatic breast cancer tissue with HA-high levels based on available tumor tissue in formaldehyde fixed-paraffin embedded (FFPE) block or minimum of ~~5 (10 preferred)~~ **10** unstained core biopsy slides that meet specific tissue sample requirements. Fine needle aspirates (FNA)**,** ~~or~~ brushing biopsies **or bone metastasis tumor samples** will not be acceptable.

Reason(s) for the Amendment:

For Inclusion Criteria #3: Study design modified to include patients in later lines based on Investigator feedback and to allow for the combination to be used in a broader patient population. Added additional details to further clarify definition of systemic anticancer therapy.

For Inclusion Criteria #4: Provide further clarification regarding the minimum number of unstained biopsy slides being requested (10)

ORIGINAL TEXT	AMENDED TEXT
SYNOPSIS and Section 9.3	***SYNOPSIS and Section 9.3***
Number of Subjects A total of approximately 96 adult female or male subjects previously treated with 0 to 1 line of systemic anticancer therapy in the metastatic setting will be enrolled (approximately 6 to 18 in the Phase 1b and 84 randomized in Phase 2 to obtain 80 evaluable in Phase 2).	**Number of Subjects** A total of approximately ~~96~~ **114** adult female or male subjects previously treated with ~~0 to 1 line~~ **up to 2 lines** of systemic anticancer therapy in the metastatic setting will be enrolled **(comprising of up to 30 in Phase 1b [**approximately 6 to 18 in the **safety run-in cohort plus 12 in the Expansion part]** and 84 randomized ~~in Phase 2~~ to obtain 80 evaluable in Phase 2).

Reason(s) for the Amendment:

Number of subjects revised due to addition of 12 subjects in the Phase 1b expansion part.

ORIGINAL TEXT	AMENDED TEXT
SYNOPSIS and Section 9.4.1.3	***SYNOPSIS and Section 9.4.1.3***
Study Treatments Dose Delays and Modifications for Eribulin Mesylate: Table 2: Eribulin Mesylate Dose Adjustments for Toxicity	Study Treatments Dose Delays and Modifications for Eribulin Mesylate: Table 2: Eribulin Mesylate Dose Adjustments for Toxicity

Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m^2	Discontinue eribulin mesylate
Unable to administer a scheduled dose of eribulin mesylate for more than 21 days of study	

Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m^2	Discontinue eribulin mesylate
If unable to administer a scheduled dose of eribulin mesylate for more than 21 days of study, **discuss with sponsor prior to continuing treatment.**	

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Reason(s) for the Amendment:

To further clarify the language and added requirement to seek Sponsor agreement prior to continuing treatment following dose delay of Eribulin Mesylate for more than 21 days.

ORIGINAL TEXT	AMENDED TEXT
SYNOPSIS and Section 9.4.1	***SYNOPSIS and Section 9.4.1***
Duration of Treatment Those subjects who will be treated with eribulin mesylate and PEGPH20 can remain on eribulin mesylate only or both study drugs in the presence of clinical benefit until unacceptable toxicity or disease progression occurs, or until the subject withdraws consent. Subjects who experience any TE event requiring full dose anti-coagulation while on PEGPH20 treatment will be discontinued from PEGPH20 treatment but may continue to receive eribulin mesylate and remain on the study.	**Duration of Treatment** Those subjects who will be treated with eribulin mesylate and PEGPH20 can remain on ~~eribulin mesylate only or~~ both study drugs in the presence of clinical benefit until unacceptable toxicity or disease progression occurs, or until the subject withdraws consent. **Discontinuing either eribulin or PEGPH20 only will be considered as study treatment discontinuation.** Subjects who experience any TE event requiring full dose anti-coagulation while on PEGPH20 treatment will be discontinued from PEGPH20 treatment but may continue to receive eribulin mesylate and remain on the study.
Reason(s) for the Amendment: *Added language to clarify the end of treatment definition.*	

ORIGINAL TEXT	AMENDED TEXT
Section 9.4.4	***Section 9.4.4***
	Added text: **The RP2D will be selected as a dose which does not exceed 1 DLT per 6 patients or 3 DLTs per 18 patients (during the DLT assessment period) and will also include assessment of the entirety of safety data including dose reductions or discontinuations that occur for either study drug during or after the DLT period.**
Reason(s) for the Amendment: *To further clarify rationale behind RP2D selection.*	

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ORIGINAL TEXT	AMENDED TEXT
Section 9.4.7.1	***Section 9.4.7.1***
Dexamethasone may be used to attenuate musculoskeletal symptoms that may occur in subjects treated with PEGPH20.	Dexamethasone ~~may be used~~ **is being given as part of the study dosing regimen in order** to attenuate musculoskeletal symptoms that may occur in subjects treated with PEGPH20.
Reason(s) for the Amendment: *To further clarify that Dexamethasone is a mandated concomitant medication in this study.*	

ORIGINAL TEXT	AMENDED TEXT
Section 9.4.7.3	***Section 9.4.7.3***
Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.	~~For~~ s~~S~~ubjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management **continuation of the study medication and further participation in the study must be discussed and agreed upon with the sponsor** ~~should be removed from the trial~~. Subjects may receive other medications that the investigator deems to be medically necessary.
Reason(s) for the Amendment: *To further specify need of Sponsor approval prior to provision of any prohibited therapies to study subjects.*	

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ORIGINAL TEXT	AMENDED TEXT
Section 9.5.1.2	***Section 9.5.1.2***
	Added text: **Additional screening assessments for Phase 1b and Phase 2 subjects will include blood samples collected for potential biomarker and plasma-HA analyses (see Section 9.5.1.6.3, Table 7, Table 8, and Table 9).**
Reason(s) for the Amendment: *For consistency with additions made in the synopsis and schedule of events*	

ORIGINAL TEXT	AMENDED TEXT
SYNOPSIS and Section 9.5.1.3	***SYNOPSIS and Section 9.5.1.3***
Assessments Definition of Dose-Limiting Toxicity: Hematologic Toxicities: • Any Grade 4 thrombocytopenia or neutropenia lasting >7 days. Nonhematologic Toxicities: • Any Grade PE or stroke. • Any Grade 4 toxicity. • Any Grade 3 toxicity EXCLUDING: o Nausea, vomiting, or diarrhea controlled by medical intervention within 72 hours. • Discontinuation or delay of more than 2 weeks of either study drug due to treatment-related AE will be considered as a DLT.	Assessments Definition of Dose-Limiting Toxicity: Hematologic Toxicities: • Any Grade 4 thrombocytopenia or neutropenia lasting >7 days. • **Neutropenia Grade 3 or 4 complicated by fever and/or infection (ANC <1.0 x 10^9/L, fever ≥38.5°C).** • **Thrombocytopenia Grade 3 complicated by bleeding and/or requiring platelet or blood transfusion**. Nonhematologic Toxicities: • Any Grade **DVT**, PE or stroke. • Any Grade 4 toxicity. • Any **clinically significant*** Grade 3 toxicity EXCLUDING: o Nausea, vomiting, or diarrhea controlled by medical intervention within 72 hours. • **Hypersensitivity reactions Grade 3 or 4 including allergy reactions or anaphylaxis symptomatic bronchospasm requiring parenteral medication(s) with or without urticaria; allergy-related**

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	edema/angioedema. • Discontinuation or delay of more than 2 weeks of either study drug due to treatment-related AE will be considered as a DLT. ***An abnormal lab value should be deemed clinically significant if either of the following conditions is met:** **• The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline.** **• The abnormality is of a degree (severity) that requires additional active management, e.g., Study drug withdraw, dose delay or omission or dose reduction, close observation and monitoring, more frequent follow-up assessments, or further diagnostic investigation.** **Therefore, a clinically significant lab value is one that indicates a new disease process, an exacerbation or worsening of an existing condition, or requires further action(s) to be taken.**

Reason(s) for the Amendment:

1) Include a "standard definition" of DLTs as defined as any of the following using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE Version 4.03),
2)Include hypersensitivity reactions as DLT , as per the IB brochure Table 35 Adverse Reaction Specification (Including Frequencies and Severities) for PEGPH20 Based on Cumulative Clinical Data (Through 2 June 2015).

ORIGINAL TEXT	AMENDED TEXT
SYNOPSIS, Section 9.5.1.5, and Section 9.5.1.5.1	***SYNOPSIS, Section 9.5.1.5, and Section 9.5.1.5.1***
Efficacy Assessments The primary endpoint (ORR), secondary endpoint (PFS), and exploratory endpoints (CBR, DCR, and DOR) will be evaluated based on tumor	**Efficacy Assessments** The primary endpoint (ORR), secondary endpoint (PFS), and exploratory endpoints (CBR, DCR, and DOR) will be evaluated based on tumor

assessments performed by the investigator. The secondary endpoint OS will be assessed throughout the study. All scans for tumor assessments performed during the study should be archived in accordance with the standard local practice. The scans must be submitted to a central core laboratory selected by the sponsor for potential central review.	assessments performed by the investigator. The secondary endpoint OS will be assessed throughout the study. ~~All scans for tumor assessments performed during the study should be archived in accordance with the standard local practice.~~ The scans must be submitted to a central core laboratory selected by the sponsor for potential central review.
Tumor assessments (CT chest and CT/MRI of abdomen, pelvis, and other areas of known disease at Screening plus any areas of newly suspected disease) should be performed at Screening (within 21 days prior to first dose of study drugs) and every6 weeks ±1 week from the date of first dose of study drug, or sooner if clinically indicated, until documentation of disease progression. Skin lesions will not be included as target lesions, but may only be considered as non-target lesions.	Tumor assessments (CT chest and CT/MRI of abdomen, pelvis, and other areas of known disease at Screening plus any areas of newly suspected disease) should be performed at Screening (within 21 days prior to first dose of study drugs) and every 6 weeks ±1 week from the date of first dose of study drug (**Phase 1b) or randomization (Phase 2)**, or sooner if clinically indicated, until documentation of disease progression. Skin lesions will not be included as target lesions, but may only be considered as non-target lesions.
A brain scan (CT with contrast or MRI pre- and post-gadolinium) must be performed at Screening (within 21 days prior to first dose of study drugs), to assess potential CNS disease and/or metastases. For the duration of the study (ie, post-Baseline), CT/MRI of the brain will be performed if clinically indicated, and within a target of 1 week after a subject achieves a complete response (CR). For subjects with a history of treated brain metastases, brain scans will be performed at tumor assessment time points, if clinically indicated.	A brain scan (CT with contrast or MRI pre- and post-gadolinium) must be performed at Screening (within 21 days prior to first dose of study drugs **[Phase 1b] or randomization [Phase 2]),** to assess potential CNS disease and/or metastases. For the duration of the study (ie, post-Baseline), CT/MRI of the brain will be performed if clinically indicated, and within a target of 1 week after a subject achieves a complete response (CR). For subjects with a history of treated brain metastases, brain scans will be performed at **all** tumor assessment time points~~, if clinically indicated~~.
A bone scan (99m-technetium polyphosphonate scintigraphy, whole body bone MRI, or 18F-NaFpositron emission tomography [PET]) to assess bone metastases should be performed within 6 weeks prior to first dose of study drugs (historical scans are acceptable) and then every 24 weeks ±1 week after the date of first dose of study drugs, or sooner if clinically indicated.	A bone scan (^{99}m-technetium **based** ~~polyphosphonate~~ scintigraphy, whole body bone MRI, or ^{18}F-NaF-positron emission tomography [PET]) to assess bone metastases should be performed within 6 weeks prior to first dose of study drugs **(Phase 1b) or randomization (Phase 2)** (historical scans are acceptable) and then every 24 weeks ±1 week after the date of first dose of study drugs **(Phase 1b) or randomization (Phase 2),** or sooner if clinically indicated.

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Confirmation is not required for best overall response (BOR) of CR or partial response (PR) in either Phase 1b or Phase 2 parts of the trial. Best overall response of stable disease (SD) requires at least 1 posttreatment assessment that meets the SD criteria ≥5 weeks after the start of treatment	Confirmation is not required for best overall response (BOR) of CR or partial response (PR) in either Phase 1b or Phase 2 parts of the trial. Best overall response of stable disease (SD) requires at least 1 posttreatment assessment that meets the SD criteria ≥5 weeks after the start of treatment **(Phase 1b) or randomization (Phase 2).**

Reason(s) for the Amendment:

Added language to a. delete contradictory language and b. specify the various intervals of tumor assessment apply to both phases of the study.

ORIGINAL TEXT

Section 9.5.1.6.1

Table 1 Blood Sample Collection for Pharmacokinetic Analysis of Eribulin and PEGPH20 for Phase 1b Subjects

Cycle / Day	PEGPH20 Sample Timepoints (n=8)	Eribulin Sample Timepoints (n=11)
C1D-1	Predose (0 h)	
	Postdose (15 min)	
	Postdose (1 h)	
	Postdose (2 h)	
	Postdose (4 h)	
C1D1[a]	Postdose (24 h)	Predose (0 h)
		Postdose (15 min)
		Postdose (30 min)
		Postdose (1 h)
		Postdose (2 h)
		Postdose (4 h)
C1D2[a]	Postdose (48 h)	Postdose (24 h)
C1D3[a]	Postdose (72 h)	Postdose (48 h)
C1D4		Postdose (72 h)
C1D5		Postdose (96 h)
C1D6		Postdose (120 h)

C=cycle; D=day; h=hour(s); min=minutes

AMENDED TEXT

Section 9.5.1.6.1

Table 2 Blood Sample Collection for Pharmacokinetic Analysis of Eribulin,andPEGPH20 **and Plasma HA analysis for** Phase 1b **Expansion Part** subjects

Cycle / Day	PEGPH20 Sample Timepoints (n=8)	Eribulin Sample Timepoints (n=11)
C1D-1	Predose (0 h) [b]	
	Postdose (15 min)	
	Postdose (1 h)	
	Postdose (2 h)	
	Postdose (4 h)	
C1D1[a]	Postdose (24 h) [b]	Predose (0 h)
		Postdose (15 min)
		Postdose (30 min)
		Postdose (1 h)
		Postdose (2 h)
		Postdose (4 h)
C1D2[a]	Postdose (48 h) [b]	Postdose (24 h)
C1D3[a]	Postdose (72 h) [b]	Postdose (48 h)
C1D4		Postdose (72 h)
C1D5		Postdose (96 h)

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a: Note that samples collected at 24, 48 and 72 hours after the PEGPH20 infusion correspond, respectively, with eribulin mesylate predose [0 hour] on Cycle 1 Day 1 [C1D1], as well as 24 and 48 hours after the infusion of eribulin mesylate. Separate PEGPH20 and eribulin blood samples will be collected at these time points. Details are provided in the Pharmacokinetics Sample Collection and Handling Manual for this study.	C1D6 | | Postdose (120 h) C=cycle; D=day; h=hour(s); min=minutes a: Note that samples collected at 24, 48 and 72 hours after the PEGPH20 infusion correspond, respectively, with eribulin mesylate predose [0 hour] on Cycle 1 Day 1 [C1D1], as well as 24 and 48 hours after the infusion of eribulin mesylate. Separate PEGPH20 and eribulin blood samples will be collected at these time points. Details are provided in the Pharmacokinetics Sample Collection and Handling Manual for this study. **b: For those time points, one PEGPH20 PK samples and one Plasma-HA sample will be collected (for more details please see Section 9.5.1.6.3 Biomarker assessment - Pharmacogenomic and Pharmacodynamic blood samples)**

Reason(s) for the Amendment:

The plasma HA sample is being added as a PD marker for PEGPH20 activity, and the additional time points are added to better characterize the PD response. Changes in plasma HA over the first 24 hours would be critical to our understanding of the pharmacological effects of PEGPH20 in this patient population.

ORIGINAL TEXT	AMENDED TEXT
*SYNOPSIS and **Section 9.5.1.6.3***	*SYNOPSIS and **Section 9.5.1.6.3***
Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Tumor Samples Archived and/or fresh (if possible) tissue samples will be obtained for all subjects at screening for assessment of HA levels. At least 5 (preferred 10) unstained, consecutive slides of one archival tumor block or paraffin block, or a fresh tumor biopsy that meet specific tissue sample requirements are required. Tumor samples collected via FNA and brushing biopsies are not acceptable. <u>Pharmacogenomic and Pharmacodynamic blood samples</u> Where not prohibited by local regulations, blood samples for all Phase 2 subjects will be collected for potential pharmacogenomic and/or	Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Tumor Samples Archived and/or fresh (if possible) tissue samples will be obtained for all subjects at screening for assessment of HA levels. At least ~~5 (preferred 10)~~ **10** unstained, consecutive slides of one archival tumor block or paraffin block, or a fresh tumor biopsy that meet specific tissue sample requirements are required. Tumor samples collected via FNA and brushing biopsies are not acceptable. <u>Pharmacogenomic and Pharmacodynamic blood samples</u> Where not prohibited by local regulations, blood samples for **Phase 1b** and ~~all~~ Phase 2 subjects will be collected for potential pharmacogenomic

pharmacodynamic analyses.	and/or pharmacodynamic analyses **as defined in the schedule of assessments.** **Phase 1b** **Blood samples from all Phase 1b Expansion Part subjects will be collected at the PEGPH20 predose on Day -2 or C1 Day -1 for potential pharmacogenomics (PGx) analyses.** **Blood samples for potential pharmacodynamics (PD) for biomarkers analyses will be collected from the Phase 1b Expansion Part subjects at the screening visit, at the PEGPH20 predose on Day -2 or C1 Day -1, C1 Day 7, C2 Day -1, Day -1 of every other cycle (C3, C5, C7, etc.), and at the End of Treatment Visit, or whenever a subject is withdrawn from study treatment.** **A sample for plasma-HA analysis of PEGPH20 will be collected from the Phase 1b expansion Part subjects on Cycle 1 Day -1 (C1 Day -1) at predose (0 hour). Additional sample will be collected at 24, 48, and 72 hours after the PEGPH20 infusion (which will correspond, respectively, with eribulin mesylate predose [0 hour] on C1D1, 24 and 48 hours after the infusion of eribulin mesylate).**
A single blood sample on Cycle 1 Day -1 will be collected at PEGPH20 pre-dose (for Phase 2/Arm A subjects) and a single sample on Cycle 1 Day 1 will be collected at eribulin mesylate pre-dose……	**Phase 2** A single blood sample on **Day -2 or** Cycle 1 Day -1 will be collected at PEGPH20 pre-dose (for Phase 2/Arm A subjects) and a single sample on **Day -1 or** Cycle 1 Day 1 will be collected at eribulin mesylate pre-dose……

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For Phase 2/Arm A subjects (samples collected at PEGPH20 pre-dose on C1 Day -1 and at the End of Treatment Visit or whenever a subject is withdrawn from the study), pharmacodynamic evaluations (eg, to study blood biomarkers and total HA disaccharide in plasma [plasma-HA]) may be performed using global proteomic methods, enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay, validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods, or other assays/methods and new technology. Samples may also be analyzed for circulating tumor DNA or miRNA. Blood biomarker samples may be used for exploratory analysis for evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development. For Phase 2/Arm B subjects (samples collected at eribulin mesylate pre-dose on C1 Day 1 and at the End of Treatment Visit or whenever a subject is withdrawn from the study), pharmacodynamics evaluations (blood biomarkers, only) may be performed as described above.	~~For Phase 2/Arm A subjects (samples collected at PEGPH20 pre-dose on C1 Day -1 and at the End of Treatment Visit or whenever a subject is withdrawn from the study),~~ For Phase 2/Arm A subjects **blood samples for potential ADA analyses will be collected at PEGPH20 predose on Day -2 or C1 Day -1 and at the End of Treatment Visit (or whenever a subject is withdrawn from the study). Blood samples for potential pharmacodynamics for plasma-HA and biomarkers analyses will be collected during screening, at PEGPH20 pre-dose on Day -2 or C1 Day -1, C1 Day 7, C2 Day -1, Day -1 of every other cycle (C3, C5, C7, etc.), and at the End of Treatment Visit or whenever a subject is withdrawn from the study).** **For Phase 2/Arm B blood samples for potential pharmacodynamics for plasma-HA and biomarkers analyses will be collected during screening, at eribulin mesylate pre-dose on C1 Day 1, C1 Day 8, C2 Day 1, Day 1 of every other cycle (C3, C5, C7, etc.), and at the End of Treatment Visit or whenever a subject is withdrawn from the study).** Pharmacodynamic evaluations (eg, to study blood biomarkers and total HA disaccharide in plasma [plasma-HA]) may be performed using global proteomic methods, enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay, validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods, or other assays/methods and new technology. Samples may also be analyzed for circulating tumor DNA or miRNA. Blood biomarker samples may be used for exploratory analysis for evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development. ~~(samples collected at eribulin mesylate pre-dose on C1 Day 1 and at the End of Treatment Visit or whenever a subject is withdrawn from the study), pharmacodynamics evaluations (blood biomarkers, only) may be performed as described above~~
Reason(s) for the Amendment:	

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Phase 1b: PGx sample added for pharmacogenomics analysis. Plasma HA sample is being added as a PD marker for PEGPH20 activity, and the additional time points are added to better characterize the PD response. Changes in plasma HA over the first 24 hours would be critical to the understanding of the pharmacological effects of PEGPH20 in this patient population. PD biomarker samples added to better characterize the PD response.

Phase 2 Arm A and Arm B: Plasma HA and Biomarkers - Additional time points added to better characterize the PD response.

ORIGINAL TEXT	AMENDED TEXT
Section 9.1.1	***Section 9.1.1***
Pretreatment/Prerandomization Phase The Baseline Period includes randomization (Phase 2 subjects only) and the Baseline Visit (all subjects). Specifically, Phase 1b and Phase 2/Arm A subjects, will have their safety and efficacy assessments performed on or before designated Study Day -1 or C1D-1, prior to administration of their first dose of PEGPH20 (see Schedule of Procedures/Assessments, Table 7 and Table 8); Phase 2/Arm B subjects will have their safety and efficacy assessments performed on or before designated Study Day 1, prior to administration of their first dose of eribulin mesylate (Table 7 see Schedule of Procedures/Assessments, Table 9).	Pretreatment/Prerandomization Phase The Baseline Period includes randomization (Phase 2 subjects only) and the Baseline Visit (all subjects). Specifically, Phase 1b and Phase 2/Arm A subjects, will have ~~their safety and efficacy~~ **Baseline** assessments performed on or before designated Study **Day -2** ~~1~~ or C1D-1, prior to administration of their first dose of PEGPH20 (see Schedule of Procedures/Assessments, **Error! Reference source not found.** and **Error! Reference source not found.**); Phase 2/Arm B subjects will have their ~~safety and efficacy~~ **Baseline** assessments performed on **Day -1 or on Cycle 1 Day 1** ~~or before designated Study Day 1~~, prior to administration of their first dose of eribulin mesylate (~~Table 7~~ see Schedule of Procedures/Assessments, **Error! Reference source not found.**).
Reason(s) for the Amendment: *For added clarity*	

Clinical Study Protocol Amendment

ORIGINAL TEXT	AMENDED TEXT
Section 9.2	***Section 9.2***
Discussion of Study Design, Including Choice of Control Groups HA-high is considered to be a poor prognostic factor for patients with metastatic disease (Tammi RH et al, Kultti A et al). Therefore, a two-arm study design is used to allow evaluation of a potential synergistic effect of the combination therapy over single agent eribulin mesylate in this patient population.	Discussion of Study Design, Including Choice of Control Groups HA-high is considered to be a poor prognostic factor for patients with metastatic disease (Tammi ~~RH~~, et al., **2008**; Kultti ~~A~~, et al., **2012**) Therefore, a two-arm study design is used to allow evaluation of a potential synergistic effect of the combination therapy over single agent eribulin mesylate in this patient population. **Following establishment of RP2D at the Phase 1b Safety run-in part of the study, a Phase 1b Expansion part consisting of 12 subjects will provide additional safety data prior to initiating the Phase 2 part of the study. This is in order to assess the safety profile of the combination and identify any potential safety signals and the incidence of thromboembolic events in this population.**
Reason(s) for the Amendment: *Language added to further explain rationale for adding the Phase 1b expansion part.*	

Clinical Study Protocol Amendment

ORIGINAL TEXT	AMENDED TEXT
Section 7.1.3.2	***Section 7.1.3.2***
Clinical Experience with PEGPH20 PEGPH20 is being developed as an investigational, novel therapeutic agent for use in combination with chemotherapy or other agents for the treatment of patients with cancers that accumulate HA. As of 02 June 2015, a total of 197 subjects have been exposed to PEGPH20 as a single agent or in the following combinations: 1) gemcitabine; 2) gemcitabine and nab-paclitaxel; 3) modified FOLFIRNOX; or 4) docetaxel. …… In an ongoing Phase 2 study in subjects with pancreatic cancer (Study HALO-109-202), 111 subjects were randomized to receive 1000 mg/m2 gemcitabine IV once weekly, 125 mg/m2 nab-paclitaxel IV once weekly, and 3.0 µg/kg PEGPH20 IV twice weekly in the first cycle and once weekly thereafter. In an ongoing Phase 1b/2 study in subjects with advanced NSCLC (Study HALO-107-201), 4 subjects have received 75 mg/m2 docetaxel and PEGPH20 3.0 µg/kg IV once every 21 days. Halozyme Therapeutics has sponsored a total of three completed studies of PEGPH20 in subjects with solid tumor malignancies (2 monotherapy and one in combination with gemcitabine), as well as one ongoing clinical study with PEGPH20 in combination with nab-paclitaxel and gemcitabine in subjects with advanced pancreatic cancer, and one ongoing clinical study with PEGPH20 in combination with docetaxel in subjects with metastatic NSCLC.	Clinical Experience with PEGPH20 PEGPH20 is being developed as an investigational, novel therapeutic agent for use in combination with chemotherapy or other agents for the treatment of patients with cancers that accumulate HA. As of ~~02 June 2015~~ **13 February 2016**, a total of ~~197~~ **272** subjects have been exposed to PEGPH20 as a single agent or in the following combinations: 1) gemcitabine; 2) gemcitabine and nab-paclitaxel; 3) modified FOLFIRNOX; or 4) docetaxel or **5) pembrolizumab**. ……In an ongoing Phase 2 study in subjects with pancreatic cancer (Study HALO-109-202), ~~111~~ **156** subjects were randomized to receive 1000 mg/m^2 gemcitabine IV once weekly, 125 mg/m^2 nab-paclitaxel IV once weekly, and 3.0 µg/kg PEGPH20 IV twice weekly in the first cycle and once weekly thereafter. In an ongoing Phase 1b/2 study in subjects with advanced NSCLC (Study HALO-107-201), ~~4~~ **10** subjects have received 75 mg/m^2 docetaxel and **various doses of PEGPH20 1.6-3.0 µg/kg IV once every 21 days. In an ongoing Phase 1b/2 study in subjects with advanced NSCLC or gastric cancer (Study HALO-107-101), 4 subjects have received 2 mg/kg IV pembroluzimab and 1.6 µg/kg IV of** PEGPH20 ~~3.0 µg/kg~~ once every 21 days.… Halozyme Therapeutics has sponsored a total of three completed studies of PEGPH20 in subjects with solid tumor malignancies (2 monotherapy and one in combination with gemcitabine), as well as one ongoing clinical study with PEGPH20 in combination with nab-paclitaxel and gemcitabine in subjects with advanced pancreatic cancer**,** ~~and~~ one ongoing clinical study with PEGPH20 in combination with docetaxel in subjects with metastatic NSCLC **and one ongoing clinical study with PEGPH20 in combination with pembroluzimab in subjects with metastatic NSCLC or gastric cancer.As of the data cutoff date of the current IB, 255 subjects (156 subjects in the PAG arm versus 99 in the AG arm) have been dosed in Study HALO-109-202. Among the PAG subjects, 74 subjects were dosed in Stage 1 and 82 in Stage 2. Among the**

AG subjects, 61 were dosed in Stage 1 and 38 in Stage 2.

Halozyme has also developed, in collaboration with a leading diagnostic company, a novel investigational co-developed diagnostic product assay which may potentially be used to identify subjects who might benefit most, based on HA tumor content, from the administration of PEGPH20 in conjunction with other cancer therapeutics. This assay uses an affinity-histochemistry-based staining method to evaluate HA levels in tumor biopsies. The CDx assay was developed in parallel with the clinical program and was used to retrospectively analyze PDA tumor samples for HA levels in Study HALO-109-202, to determine its predictive value. A tumor is determined to be HA-high when the extracellular tumor matrix, over the entire tumor surface stained at ≥50%.

Final efficacy data (with a data cut of December 2014) for subjects in Stage 1 of Study HALO-109-202 using the Ventana HA CDx assay and scoring algorithm are presented below:

A total of 135 subjects were treated (74 PAG, 61 AG), of which 118 subjects (66 PAG and 52 AG) had evaluable HA data. PFS results are shown below (median follow-up was 7 months). In HA-high subjects receiving PAG versus AG, ORR was 55% (1 CR) versus 33%.

	mPFS, mo		
Population	**PAG**	**AG**	**Hazard Ratio [95% CI]**
Treated	**5.5 (n=74)**	**5.2 (n=61)**	**0.73 [0.46-1.15]**
HA-High (n=43 w/ evaluable	**9.2 (n=22)**	**6.3 (n=21)**	**0.48 [0.16-1.48]**

HA data)			
HA-Low (n=75 w/ evaluable HA data)	**5.3 (n=44)**	**4.3 (n=31)**	**0.69 [0.38-1.25]**

In conclusion, clinically meaningful improvements in PFS, and ORR was observed in subjects with HA-high tumors receiving PAG versus AG.

Final safety and efficacy analyses including Stage 2 patients is pending data maturation.

Preliminary efficacy data for subjects in Stage 1 of Study HALO-109-202 in 146 total patients were presented at the American Society of Clinical Oncology Meeting in May 2015. A total of 41% of PAG subjects and 34% of AG subjects have had a complete or partial response, with a median duration of response at 7.4 months on PAG and 4.2 months on AG. Subjects with HA-high tumors on PAG had a 15% higher response rate than those with HAlow tumors with a duration of response at 8.1 months, versus 5.8 months, respectively. There was no difference in response rate between HA-high or HA-low for subjects on AG.

~~Preliminary efficacy data for subjects in Stage 1 of Study HALO-109-202 in 146 total patients were presented at the American Society of Clinical Oncology Meeting in May 2015. A total of 41% of PAG subjects and 34% of AG subjects have had a complete or partial response, with a median duration of response at 7.4 months on PAG and 4.2 months on AG. Subjects with HA-high tumors on PAG had a 15% higher response rate than those with HAlow tumors with a duration of response at 8.1 months, versus 5.8 months, respectively. There was no difference in response rate between HA-high or HA-low for subjects on AG.~~

In regards to PFS, PAG subjects had a median PFS of 5.7 months versus 5.2 months for AG. When assessing for subjects with HA data, there was a statistically significant difference in PFS between subjects with HA-high on PAG (9.2 months) vs AG (4.3 months). Subjects on PAG with HA-high tumors had an almost 4 month increase in PFS as compared to those with HA-low tumors (9.2 months vs 5.3 months, respectively). In regards to AG subjects, there was no significant difference between the two HA scores (HA-high: 4.3 months vs HA-low: 5.6 months). Preliminary overall survival from 23 subjects on PAG and 21 on AG is 12 months and 9 months, respectively.

~~In regards to PFS, PAG subjects had a median PFS of 5.7 months versus 5.2 months for AG. When assessing for subjects with HA data, there was a statistically significant difference in PFS between subjects with HA-high on PAG (9.2 months) vs AG (4.3 months). Subjects on PAG with HA-high tumors had an almost 4 month increase in PFS as compared to those with HA-low tumors (9.2 months vs 5.3 months, respectively). In regards to AG subjects, there was no significant difference between the two HA scores (HA-high: 4.3 months vs HA-low: 5.6 months). Preliminary overall survival from 23 subjects on PAG and 21 on AG is 12 months and 9 months, respectively.~~

A total of 238 subjects (93%) have experienced a treatment-emergent AE (TEAE) up to 13 Feb 2016 (Data cutoff for the Investigator's brochure) and 230 subjects (90%) have experienced at least 1 TEAE related to study

	drug. Overall, the most commonly reported SOCs were gastrointestinal disorders (221 subjects [87%]), general disorders and administration site conditions (216 subjects [85%]), metabolism and nutritional disorders (175 subjects [69%]), and musculoskeletal and connective tissue disorders (164 subjects [64%]).
	In terms of safety, the most common PEGPH20 treatment-related AEs (≥10%) by preferred term (PT) were muscle spasms (79 subjects [51%]), fatigue (72 subjects [46%]), peripheral edema (56 subjects [36%]), myalgia (34 subjects [22%]), nausea (30 subjects [19%]), arthralgia (29 subjects [19%]), decreased appetite (27 subjects [17%]), diarrhea (27 subjects (17%)], vomiting (22 subjects (14%)], dysgeusia (20 subjects [13%], abdominal pain (16 subjects [10%]) ALT increased (16 subjects [10%]), and asthenia (15 subjects [10%]).
In terms of safety, the most common PEGPH20 treatment-related AEs (≥10%) by preferred term (PT) were muscle spasms (53%), fatigue (51%), peripheral edema (37%), myalgia (23%), nausea (23%), arthralgia (21%), diarrhea (20%), decreased appetite (19%), vomiting (16%), alanine aminotransferase (ALT) increased (15%), aspartate aminotransferase (AST) increased (14%), anemia (14%), dysgeusia (14%), asthenia (14%), dysphonia (12%), thrombocytopenia (12%), platelet count decreased (11%), neutropenia (11%), and hypoalbuminemia (10%).	~~In terms of safety, the most common PEGPH20 treatment-related AEs (≥10%) by preferred term (PT) were muscle spasms (53%), fatigue (51%), peripheral edema (37%), myalgia (23%), nausea (23%), arthralgia (21%), diarrhea (20%), decreased appetite (19%), vomiting (16%), alanine aminotransferase (ALT) increased (15%), aspartate aminotransferase (AST) increased (14%), anemia (14%), dysgeusia (14%), asthenia (14%), dysphonia (12%), thrombocytopenia (12%), platelet count decreased (11%), neutropenia (11%), and hypoalbuminemia (10%).~~
In Stage 2 of the study, after the protocol was amended to include prophylaxis with enoxaparin, the TE event rate was reduced. An analysis of TE events as of May 2015 in the ongoing Stage 2 portion indicated a TE event rate of 28% (n = 18) in the PAG group vs 29% (n = 7) in the AG group for subjects who either initiated enoxaparin at 40 mg/day or initiated at 40 mg/day and increased to 1 mg/kg/day; and no TE events for subjects who initiated enoxaparin at 1 mg/kg/day were reported in the PAG group (n = 20) vs 10% in the AG group (n = 10).	In Stage 2 of the study, after the protocol was amended to include prophylaxis with enoxaparin, the TE event rate was reduced. An analysis of TE events as of ~~May 2015~~ **February 2016** in the ongoing Stage 2 portion indicated a TE event rate of 28% (n = 18) in the PAG group vs 29% (n = 7) in the AG group for subjects who either initiated enoxaparin at 40 mg/day or initiated at 40 mg/day and increased to 1 mg/kg/day; **the incidence for subjects who have started on enoxaparin at 1 mg/kg/day was 9% for PAG subjects (n=68) vs 5% versus for AG subjects (n=38)** ~~and no TE events for subjects who initiated enoxaparin at 1 mg/kg/day were reported in the PAG group (n =~~

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	~~20) vs 10% in the AG group (n = 10).~~ **As of 13 February 2016, 10 subjects have been dosed with PEGPH20 (6 subjects with 1.6 µg/kg of PEGPH20 and 4 subjects with 3.0 µg/kg of PEGPH20) and docetaxel once every 21 days. All subjects (N=10) have experienced at least one TEAE. Overall, the most commonly reported SOCs (SOCs experienced by ≥50% of subjects) were musculoskeletal and connective tissue disorders (90%), general disorders and administration site conditions (80%), respiratory, thoracic, and mediastinal disorders (80%), blood and lymphatic system disorders (60%), gastrointestinal disorders (60%), and nervous system disorders (60%). The most common treatment emergent adverse events (by preferred term) were myalgia (70%), fatigue (70%), muscle spasms (50%), and nausea (50%).** **Phase 1b/2 Study HALO-107-101: This an ongoing Phase 1b/2 study to evaluate the combination of pembrolizumab and PEGPH20 in previously treated Stage IIIB or IV NSCLC subjects having failed at least 1 previous platinum containing chemotherapy regimen for locally advanced or metastatic disease and subjects with recurrent locally advanced or metastatic gastric adenocarcinoma having failed at least 1 previous chemotherapy regimen. In Phase 1b pembrolizumab in combination with a fixed dose of pembrolizumab (2mg/kg) will be investigated starting at 1.6 µg/kg with increasing cohorts of 2.2, 3.0, and 4.0 µg/kg per standard dose escalation design. The Phase 2 portion of the study will further study the recommended Phase 2 dose of pembrolizumab combined with PEGPH20 in the 2 study populations separately in order to assess additional safety and preliminary efficacy. The study is currently enrolling in Phase 1b. A total of 4 patients were enrolled as of the date of cutoff of the current IB.**
Reason(s) for the Amendment: *Amended per recent data from Halozyme studies on PEGPH20*	

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ORIGINAL TEXT	AMENDED TEXT
Section 9.2.1.1	***Section 9.2.1.1.1***
	Section ***9.2.1.1.1*** Thromboembolic Events Added following sub-section *Section 9.2.1.1.1* THROMBOEMBOLIC EVENTS IN BREAST CANCER **The clinical evidence for the use of enoxaparin prophylaxis in outpatients with breast cancer is not sufficiently proven, and carries a risk of additional safety for the risk of bleeding. When deciding whether to use primary antithrombotic prophylaxis in ambulatory cancer patients receiving chemotherapy, a clinician needs to determine the patient's baseline risk of VTE and weigh the magnitude of benefit with antithrombotic prophylaxis, especially on major clinical endpoints, against the risk of bleeding.** **Breast cancer was associated with the lowest risk of VTE among average-risk groups (5 per 1,000 person-years), but among those at high risk of VTE, this rose to 55 per 1,000 person-years. Approximately 1% of breast cancer patients developed VTE within 2 years, with the highest incidence in the first 6 months after diagnosis. Metastatic disease and comorbidities were the strongest predictors. The diagnosis of VTE was associated with a higher risk of death within 2 years. Specifically, a higher incidence of VTE has been reported in patients receiving tamoxifen therapy (0.9%), chemotherapy (2.1%), and the combination (4% to 13%), in either early stage1-4 or advanced breast cancer (4.4%) (Chew, et al., 2007)** **Routine thromboprophylaxis is not recommended for patients with cancer in the outpatient setting. It may be considered for selected high-risk patients. LMWH is recommended for the initial 5 to 10 days of treatment for DVT and PE as well as for long-term secondary prophylaxis (at least 6 months). Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE because of limited data**

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	in patients with cancer. Anticoagulation should not be used to extend survival of patients with cancer in the absence of other indications. (Lyman, et al., 2013).

Reason(s) for the Amendment:

Added additional data regarding incidence of TE in mBC and the rationale a. for including expansion part in Phase 1b and b. for not mandating prophylaxis in this population.

ORIGINAL TEXT	AMENDED TEXT
Section 9.2.1.4 Risk Mitigation Plans	***Section 9.2.1.4 Risk Mitigation Plans***
To reduce the potential for TE events during the study, subjects will be excluded during screening if they have prior history or current evidence of DVT, PE, CVA, TIA, hereditary thrombophilic syndromes, or active carotid artery disease requiring treatment. Also, subjects who experience any TE event requiring full dose anti-coagulation while on PEGPH20 treatment will be discontinued from PEGPH20 treatment but may continue to receive eribulin mesylate and remain on study. Since the risk for MSEs are previously known to be low in various eribulin mesylate MBC studies (Studies 301, 305, and 206), dexamethasone premedication will be required for the combination treatment arm (eribulin mesylate and PEGPH20), only. To reduce the potential for immunosuppressive effects that might lead to hematologic toxicity and/or infections, pretreatment with dexamethasone will be limited to the same day as PEGPH20 infusion (2 hours before and 8 to 12 hours after).	To reduce the potential for TE events during the study, subjects will be excluded during screening if they have prior history or current evidence of DVT, PE, CVA, TIA, atrial fibrillation, hereditary thrombophilic syndromes, or active carotid artery disease requiring treatment. **Subjects with prior history and/or clinical evidence of venous thromboembolism (VTE) during screening or venous thromboembolism High Clinical Risk Khorana score ≥3 will also be excluded from the study**. **An Expansion Part of 12 subjects in the phase 1b part of the study will allow further monitoring of the TE events and other risks. Following completion of one treatment cycle by the Expansion Part subjects, a safety evaluation of all Phase 1b subjects, focusing on incidence of TE events, will be conducted prior to proceeding with the Phase 2 part of the study. If more than 2 TE events occurs in 18 subjects in Phase 1b then the sponsor in collaboration with Halozyme will decide on further required changes to the study conduct.** ~~Also, but may continue to receive eribulin mesylate and remain on study~~Since the risk for MSEs are previously known to be low in various eribulin mesylate MBC studies (Studies 301, 305, and 206), dexamethasone premedication will be required for the combination treatment arm (eribulin mesylate and PEGPH20), only. To reduce the potential for immunosuppressive effects that might lead to hematologic toxicity and/or infections, pretreatment with dexamethasone will be limited to the same day as PEGPH20 infusion (2 hours before and 8 to 12 hours after).

Reason(s) for the Amendment:

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Added language to further clarify rational for excluding patients with high risk of VTE and reason for addition of the Phase 1b Expansion part (appropriate measures to improve the TE risk minimization of the combination treatment).

ORIGINAL TEXT	AMENDED TEXT
SYNOPSIS and ***Section 9.3.2***	***SYNOPSIS and Section 9.3.2***
Exclusion Criteria 5. Previous history or current evidence of deep vein thrombosis (DVT), hereditary thrombophilic syndromes, pulmonary embolism (PE), cerebral vascular attack (CVA), transient ischemic attack (TIA), or active carotid artery disease requiring treatment**.**	Exclusion Criteria 5. Previous history or current evidence of deep vein thrombosis (DVT), hereditary thrombophilic syndromes, pulmonary embolism (PE), cerebral vascular **accident** ~~attack~~ (CVA), transient ischemic attack (TIA), **atrial fibrillation [AF]** or active carotid artery disease requiring treatment. 6. **Patients with prior history and or clinical evidence of venous thromboembolism (VTE) during screening or VTE High Clinical Risk Khorana score ≥3 (Appendix 7)**
6. Treatment with hormonal or biological therapy within the previous 3 weeks, radiation or small molecule targeted therapy within the previous 2 weeks.	8. Treatment with **chemotherapy,** hormonal or biological therapy within the previous 3 weeks, radiation or small molecule targeted therapy within the previous 2 weeks **preceding informed consent.**
18. Females of childbearing potential who: □ Do not agree to use a highly effective method of contraception (eg, total abstinence [if it is their preferred and usual lifestyle], an intrauterine device, a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) within 30 days before study entry and throughout the entire study period or for 28 days after study drug discontinuation. □ Are currently totally abstinent (as their preferred and usual lifestyle), and who do not agree to continue to be totally abstinent during the study period or for 28 days after study drug discontinuation. □ Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study or for 28 days after study drug discontinuation.	19. Females of childbearing potential who: • Do not agree to use a highly effective method of contraception (ie, total abstinence [if it is their preferred and usual lifestyle], an intrauterine device **(IUD) or intrauterine system (IUS)**, a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) within 30 days before study entry and throughout the entire study period ~~or~~ **and** for **3 months** ~~28 days~~ after study drug discontinuation. **For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, i.e., double barrier methods of**

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	contraception such as a condom plus diaphragm or cervical vault cap with spermicide. • Are currently totally abstinent (as their preferred and usual lifestyle), and who do not agree to continue to be totally abstinent during the study period ~~or~~ **and** for **3 months** ~~28 days~~ after study drug discontinuation. • Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study ~~or~~ **and** for **3 months** ~~28 days~~ after study drug discontinuation.
19. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or using effective contraception throughout the study period or for 28 days after study drug discontinuation). No sperm donation is allowed during the study period or for 28 days after study drug discontinuation.	**20.** Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or using effective contraception throughout the study period ~~or for 28 days~~ **and for 3 months** after study drug discontinuation). No sperm donation is allowed during the study period ~~or for 28 days~~ **and for 3 months** after study drug discontinuation.

Reason(s) for the Amendment:

For Exclusion Criteria #5: Subjects with history of atrial fibrillation [AF] is added for safety consideration

For Exclusion Criteria #6: Exclude Patients with VTE High Clinical Risk based on the Khorana score1 for safety consideration

For Inclusion Criteria #8: prior chemotherapy is added, as standard definition of population in this setting

For Inclusion Criteria #19: For outside EU sites, permissible method of contraception is added. According to the EMA CTFG recommendations on contraception in clinical trials, for authorised products the period of time that contraception is required should match the SmPC which recommends 3 months.

For Inclusion criteria #20: Male contraception is usually not required for eribulin monotherapy studies. For this protocol male contraception is recommended for PEGPH20.

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ORIGINAL TEXT	***AMENDED TEXT***
SYNOPSIS and ***Section 9.7.2***	*SYNOPSIS and* ***Section 9.7.2***
Statistical Methods (Analysis Sets) • Definitions of Analysis Sets The evaluable analysis set (EAS) includes all subjects randomized to Phase 2 who had at least 1 dose of the study drug and had both an evaluable baseline tumor assessment and an evaluable postbaseline tumor assessment, unless discontinued early because of disease progression or death (within 91 days of randomization). It is the primary analysis set for the primary efficacy endpoint, ORR.	**Statistical Methods (Analysis Sets)** • Definitions of Analysis Sets The evaluable analysis set (EAS) includes all subjects randomized to Phase 2 who had at least 1 dose of the study drug and had both an evaluable baseline tumor assessment and an evaluable postbaseline tumor assessment, unless discontinued early **or death** ~~(within 91 days of randomization~~). It is the primary analysis set for the primary efficacy endpoint, ORR.
Reason(s) for the Amendment: *Using the modified evaluable analysis set will more accurately estimate the primary efficacy endpoint (ORR).*	

ORIGINAL TEXT	***AMENDED TEXT***
Section 9.5.4.2	*Section 9.5.4.2*
Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.	Any pregnancy **(including pregnancy in the partner of a male subject)** in which the estimated date of conception is either before the last visit or within **3 months** ~~28 days~~ of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.
Reason(s) for the Amendment: *Language added to align with the safety reporting plan for the study*	

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ORIGINAL TEXT	***AMENDED TEXT***
Section 9.7.1.1.1	*Section 9.7.1.1.1*
• The primary endpoint of Phase 1b is the RP2D of the eribulin mesylate and PEGPH20 combination. The efficacy endpoint(s) described below will be summarized and listed by dose level based on the safety analysis set (SAS). No statistical comparison will be performed.	• The primary endpoint of Phase 1b is the RP2D of the eribulin mesylate and PEGPH20 combination. The efficacy endpoint(s) described below will be summarized and listed by dose level based on the safety analysis set (~~SAS~~). No statistical comparison will be performed.
Reason(s) for the Amendment: *Administrative*	

ORIGINAL TEXT	***AMENDED TEXT***
SYNOPSIS and Section 9.7.1.2	*SYNOPSIS and Section 9.7.1.2*
• The DLT Evaluable Set includes subjects enrolled in Phase 1b who complete the first treatment cycle (ie, take at least 2 doses of eribulin mesylate and PEGPH20 with no more than 1 dose reduction) and have sufficient safety evaluation. Subjects who had a DLT event will be considered evaluable for the DLT as well. It is the analysis set for DLT evaluation in the Phase 1b part of the study. • The Evaluable Analysis Set (EAS) includes all subjects randomized to Phase 2 who had at least 1 dose of the study drug and had both an evaluable baseline tumor assessment and an evaluable postbaseline tumor assessment, unless discontinued because of disease progression or death (within 91 days of randomization). It is the primary analysis set for the primary efficacy endpoint, ORR.	The DLT Evaluable Set includes subjects enrolled in Phase 1b who complete the first treatment cycle (ie, take at least 2 doses of eribulin mesylate and PEGPH20 with no more than 1 dose reduction) and have sufficient safety evaluation. ~~Subjects who had a DLT event will be considered evaluable for the DLT as well.~~ It is the analysis set for DLT evaluation in the Phase 1b part of the study. • The Evaluable Analysis Set (EAS) includes all subjects randomized to Phase 2 who had at least 1 dose of the study drug and had both an evaluable baseline tumor assessment and an evaluable postbaseline tumor assessment, unless discontinued **early** ~~because of disease progression~~ **or death** (~~within 91 days of randomization~~). It is the primary analysis set for the primary efficacy endpoint, ORR.
Reason(s) for the Amendment: *Using the modified evaluable analysis set will more accurately estimate the primary efficacy endpoint (ORR).*	

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ORIGINAL TEXT	*AMENDED TEXT*
SYNOPSIS and Section 9.7.1.6.1	*SYNOPSIS and Section 9.7.1.6.1*
Primary Efficacy Analysis Phase 1b The study will include at least 1 safety run-in cohort in which 6 metastatic subjects (any HA level) will receive PEGPH20 3 µg/kg on Days -1 and 7 of a 21-day cycle followed approximately 24 (±4) hours later by eribulin mesylate 1.4 mg/m^2 (dose level 1). Subjects will be observed for DLT in the first cycle. The purpose of the safety run-in cohort(s) is to study safety of the 2-drug combination. Phase 2 will proceed with dose level 1 when no more than 1 subject has a DLT. Otherwise, an eribulin mesylate dose of 1.4 mg/m^2 and PEGPH20 1.6 µg/kg will be evaluated in another cohort of 6 subjects. If no more than 1 subject has a DLT, the Phase 2 part will proceed with dose level 0 as the RP2D. Otherwise, alternative doses (eg dose level -1: eribulin mesylate 1.1 mg/m^2 and PEGPH20 1.6µg/kg) will be explored prior to the start of the Phase 2 part.	Primary Efficacy Analysis Phase 1b The study will include at least 1 safety run-in cohort in which 6 metastatic subjects (any HA level) will receive PEGPH20 3µg/kg on Days -1 and 7 of a 21-day cycle followed approximately 24 (± 4) hours later by eribulin mesylate 1.4 mg/m^2 (dose level 1). Subjects will be observed for dose-limiting toxicity in the first cycle. The purpose of the safety run-in cohort(s) is to study **the** safety of the 2-drug combination **and determine a recommended Phase 2 dose (RP2D)**. The Phase ~~2~~ **1b Expansion Part** will proceed with dose level 1 when no more than 1 subject has a DLT. Otherwise, an eribulin mesylate dose of 1.4 mg/m^2 and PEGPH20 1.6 µg/kg will be evaluated in another cohort of 6 subjects. If no more than 1 subject has a DLT, the ~~Phase 2~~**Phase 1b Expansion Part** will proceed with dose level 0 as the RP2D. Otherwise, alternative doses (eg, dose level -1: eribulin mesylate 1.1 mg/m^2 and PEGPH20 1.6µg/kg) will be explored prior to the start of the ~~Phase 2~~ **Phase 1b Expansion** part. **Following completion of one treatment cycle by the Expansion Part subjects, a safety evaluation of all Phase 1b subjects, focusing on incidence of TE events, will be conducted prior to proceeding with the Phase 2 part of the study** **If ≤1 out of 18 subjects experience a DLT, the upper limit of the 1-sided 80% exact CI for the true DLT rate will not be greater than 15.7%. If ≤2 out of 18 subjects experience a TE event, the upper limit of the 1-sided 80% exact CI for the true TE rate will not be greater than 22.3%. If more than 2 TE events occurs in 18 subjects in Phase 1b, then the sponsor in collaboration with Halozyme will decide on further required changes to the study conduct.** Phase 2

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Phase 2 The null hypotheses of no difference in ORR (H_0: ORR_{EP}=ORR_E) will be tested using normal approximation to binomial test with a two-sided significance level of 0.05, where ORR_{EP} and ORR_E are the ORR in eribulin and PEGPH20 combination and eribulin arm, respectively. It is the primary test for ORR. Two-sided 95% confidence intervals (CI) of the ORR differences will be calculated using normal approximation to binomial distribution. The superiority of combination arm will be demonstrated if the lower bound of the 95% CI is above zero. Clopper-Pearson 95% CIs of ORR will be constructed for each arm	The null hypotheses of no difference in ORR (H_0: ORR_{EP}=ORR_E) will be tested using normal approximation to binomial test with a ~~two~~ **one**-sided significance level of ~~0.05~~ **0.10**, where ORR_{EP} and ORR_E are the ORR in eribulin and PEGPH20 combination and eribulin arm, respectively. It is the primary test for ORR. Two-sided ~~95%~~**80%** confidence intervals (CI) of the ORR differences will be calculated using normal approximation to binomial distribution. ~~The superiority of combination arm will be demonstrated if the lower bound of the 95%**80%** CI is above zero.~~ Clopper-Pearson ~~95%~~**80%** CIs of ORR will be constructed for each arm
Reason for Amendment: *Language revised to align section with changes in the study design*	
ORIGINAL TEXT	***AMENDED TEXT***
Section 9.7.1.7.2	*Section 9.7.1.7.2*
PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES Pharmacodynamic and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate analysis plan.	PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES ~~Pharmacodynamic and other biomarker analyses may be performed and reported separately~~. **Pharmacodynamic and other biomarker analyses including soluble and/or tissue exploratory biomarkers (baseline and/or post-treatment) will be summarized using descriptive statistics and may be correlated with PK, and clinical outcomes-related endpoints for safety and/or efficacy as appropriate**. Details of these analyses ~~may~~ **will** be described in a separate analysis plan.
Reason for Amendment: *To add more clarity regarding Pharmacodynamic and other biomarker analyses.*	

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ORIGINAL TEXT	***AMENDED TEXT***
SYNOPSIS and ***Section 9.7.2***	*SYNOPSIS and* ***Section 9.7.2***
Statistical Methods (Analysis Sets) • Definitions of Analysis Sets • The DLT Evaluable Set includes subjects enrolled in Phase 1b who complete the first treatment cycle (ie, take at least 2 doses of eribulin mesylate and PEGPH20 with no more than 1 dose reduction) and have sufficient safety evaluation. Subjects who had a DLT event will be considered evaluable for the dose-limiting toxicity as well. It is the analysis set for DLT evaluation in the Phase 1b part of the study. The evaluable analysis set (EAS) includes all subjects randomized to Phase 2 who had at least 1 dose of the study drug and had both an evaluable baseline tumor assessment and an evaluable postbaseline tumor assessment, unless discontinued early because of disease progression or death (within 91 days of randomization). It is the primary analysis set for the primary efficacy endpoint, ORR. The SAS includes subjects who received at least 1 dose of the study drug in either Phase 1b or Phase 2. This is the analysis set for all safety evaluations.	**Statistical Methods (Analysis Sets)** • Definitions of Analysis Sets • The DLT Evaluable Set includes subjects enrolled in Phase 1b who complete the first treatment cycle (ie, take at least 2 doses of eribulin mesylate and PEGPH20 with no more than 1 dose reduction) and have sufficient safety evaluation. ~~Subjects who had a DLT event will be considered evaluable for the dose-limiting toxicity as well.~~ It is the analysis set for DLT evaluation in the Phase 1b part of the study. The evaluable analysis set (EAS) includes all subjects randomized to Phase 2 who had at least 1 dose of the study drug and had both an evaluable baseline tumor assessment and an evaluable postbaseline tumor assessment, unless discontinued ~~because of disease progression or death (within 91 days of randomization) or death)~~ **early or death.** It is the primary analysis set for the primary efficacy endpoint, ORR. The **Safety Analysis Set** ~~SAS~~ includes subjects who received at least 1 dose of the study drug in either Phase 1b or Phase 2. This is the analysis set for all safety evaluations.
Reason(s) for the Amendment: *Using the modified evaluable analysis set will more accurately estimate the primary efficacy endpoint (ORR).*	

ORIGINAL TEXT	***AMENDED TEXT***
SYNOPSIS and ***Section 9.7.2***	*SYNOPSIS and* ***Section 9.7.2***
The sample size calculation is based on the comparisons of the primary endpoint ORR. Assuming ORREP =0.63 and ORRE =0.29, 40 evaluable subjects per arm provide a power of 0.877 in testing of ORREP vs ORRE when using normal approximation to binomial test with a two-sided significance of 0.05. For the testing of PFS, it is assumed that HR of PFS in combination arm vs single arm eribulin mesylate is 0.5 (median PFS 6.8 months vs 13.6 months). Assuming a uniform	The sample size calculation is based on the comparisons of the primary endpoint ORR. Assuming ORR_{EP} =~~0.63~~ **0.35** and ORR_{E} =~~0.29~~ **0.15**, 40 evaluable subjects per arm provide a power of ~~0.877~~ **0.800** in testing of ORR_{EP} vs ORR_{E} when using normal approximation to binomial test with a ~~two~~ **one**-sided significance of ~~0.05~~ **0.10**. ~~For the testing of PFS, it is assumed that HR of PFS in combination arm vs single arm eribulin mesylate is 0.5 (median PFS 6.8 months~~

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enrollment rate of 80 evaluable subjects over 18 months, 58 PFS events are expected after 9 month follow-up which shows a power of 0.84 in a log rank test with one-sided alpha of 0.05. Approximately 96 subjects will be enrolled in the trial, including 12 in the Phase 1b part and 84 in the Phase 2 part.	~~vs 13.6 months). Assuming a uniform enrollment rate of 80 evaluable subjects over 18 months, 58 PFS events are expected after 9 month follow-up which shows a power of 0.84 in a log rank test with one-sided alpha of 0.05. Approximately 96 subjects will be enrolled in the trial, including 12 in the Phase 1b part and 84 in the Phase 2 part.~~ **A total of up to 114 subjects will be enrolled in the trial, comprising of up to 30 in the Phase 1b part (6 to 18 in the safety run-in cohort plus 12 in the Expansion part) and 84 in the Phase 2 part (to obtain 80 evaluable subjects).**
Reason(s) for the Amendment: *The protocol was revised to include third line patients; hence, the null and alternative hypotheses were adjusted correspondingly. Sample size determination was updated according to the new hypotheses.*	

ORIGINAL TEXT	***AMENDED TEXT***
SYNOPSIS and Section 9.7.3	***SYNOPSIS and Section 9.7.3***
Interim Analysis In the EAS, at least two more responders in the combination arm are required to cross the interim threshold. Using Bayesian predictive power, a minimum difference of 2 responders corresponds to an average predictive probability of 0.294 when observed ORR_{EP} is between 0.33 and 0.66. Simulation results show that the probabilities of passing interim analysis threshold are 0.912 under H_a and 0.278 under H_0.	Interim Analysis In the EAS, at least ~~two~~ **one** more responder~~s~~ in the combination arm ~~are~~ **is** required to cross the interim threshold. Using Bayesian predictive power, a minimum difference of ~~2~~**one** responder corresponds to an average predictive probability of ~~0. 294~~ **0.149** when observed ORR_{EP} is between ~~0. 33~~ **0.26** and ~~0. 66~~ **0.40**. Simulation results show that the probabilities of passing interim analysis threshold are ~~0. 912~~ **0.8583** under H_a and ~~0. 278~~ **0.3913** under H_0.
If fewer than 2 additional responders are observed in the combination arm, enrollment will be halted and assessment of other efficacy and safety parameters will be carried out before making the final interim decision, ie, restarting enrollment or terminating the trial. This scenario renders a predictive power of 0.147. The estimated probabilities of observing ≥1 responder difference between two treatment arms are 0.962 under H_a and	~~If fewer than 2 additional responders are observed in the combination arm, enrollment will be halted and assessment of other efficacy and safety parameters will be carried out before making the final interim decision, ie, restarting enrollment or terminating the trial. The predictive probability is 0.160~~ **0.1505** ~~if only one additional responder is observed in the combination arm. The estimated probabilities of observing ≥1 responder difference between two treatment arms are 0. 946~~ **0.9402**

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0.419 under H_0.	~~under H_a and 0. 405~~ **~~0.3933~~** ~~under H_0.~~

Reason(s) for the Amendment:

The protocol was revised to include the second and third line patients; hence, the null and alternative hypotheses were adjusted correspondingly. Sample size determination was updated according to the new hypotheses.

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ORIGINAL TEXT	*AMENDED TEXT*
Table 7 Schedule of Procedures/Assessment	***Table 7 Schedule of Procedures/Assessment***
	Two additional rows added within the schedule of procedures/assessment: **(1) Blood samples for potential PGx in Phase 1b Expansion Part[s]** **(2) Blood sample for plasma-HA analysis in Phase 1b Expansion Part[s]** **(3) Blood samples for PD (biomarkers) in Phase 1b Expansion Part [s]** Footnotes were revised after adding new footnote s.
Footnote g: At least 5 (preferred 10) unstained, consecutive slides of one archival tumor block or paraffin block, or a fresh tumor biopsy that meet specific tissue sample requirements are required. Any remaining tumor tissues not used for determination of HA level may be used for potential assessment of mutations and other genetic alterations or genes that may be important in the development and progression of cancer as well as for potential use in diagnostic development.	Footnote g: At least ~~5 (preferred 10)~~ **10** unstained, consecutive slides of one archival tumor block or paraffin block, or a fresh tumor biopsy that meet specific tissue sample requirements are required. Any remaining tumor tissues not used for determination of HA level may be used for potential assessment of mutations and other genetic alterations or genes that may be important in the development and progression of cancer as well as for potential use in diagnostic development.
Footnote i: Single 12-lead ECG will be performed at screening, C1 Day 1, C1 Day 8, and as clinically indicated during the study. Electrocardiograms obtained at C1 Day1 and C1 Day 8 should be performed just prior to and immediately after receiving the eribulin mesylate infusion. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.	Footnote i: ~~Single~~ 12-lead ECG will be performed at screening, C1 Day 1, C1 Day 8, and as clinically indicated during the study. Electrocardiograms obtained at C1 Day1 and C1 Day 8 should be performed just prior to and immediately after receiving the eribulin mesylate infusion. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.
	New Footnote s: **Blood samples for all Phase 1b subjects will be collected at the PEGPH20 predose on Day -2 or C1 Day -1 for potential pharmacogenomics (PGx) analyses. Blood samples for potential pharmacodynamics (PD) biomarkers analyses will be collected during screening, at the PEGPH20 predose on Day -2 or C1 Day -1, C1 Day 7, C2 Day -1, Day -1 of every other cycle (C3, C5, C7, etc), and at the End of Treatment**

	Visit, or whenever a subject is withdrawn from study treatment. **A sample for plasma-HA analysis of PEGPH20 will be collected from the Phase 1b expansion Part subjects on Cycle 1 Day -1 (C1 Day -1) at predose (0 hour). Additional sample will be collected at 24, 48, and 72 hours after the PEGPH20 infusion (which will correspond, respectively, with eribulin mesylate predose [0 hour] on C1D1, 24 and 48 hours after the infusion of eribulin mesylate).**
Footnote v: Tumor assessments will be performed using RECIST 1.1. Assessments are to be performed at the site by appropriately qualified personnel at each time point and results of the site interpretation are to be recorded on the appropriate CRFs. Historical standard of care scans that are performed with scanning parameters consistent with the requirements for this protocol within 21 days prior to dosing are acceptable. Tumor assessments (CT chest and CT/MRI of abdomen, pelvis, and other areas of known disease at Screening plus any areas of newly suspected disease) should be performed at Screening (within 21 days prior to first dose of study drugs and every 6 weeks ±1 week from the date of enrollment or sooner if clinically indicated, until documentation of disease progression. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks, until (1) the start of new anticancer treatment, (2) disease progression (3) death, or (4) the end of the study, or withdrawal of consent, whichever occurs first. Confirmation is not required for best overall response (BOR) of CR or PR in either Phase 1b or Phase 2 parts of the trial.	Footnote ~~v~~ w: Tumor assessments will be performed using RECIST 1.1. Assessments are to be performed at the site by appropriately qualified personnel at each time point and results of the site interpretation are to be recorded on the appropriate CRFs. Historical standard of care scans that are performed with scanning parameters consistent with the requirements for this protocol within 21 days prior to dosing are acceptable. Tumor assessments (CT chest and CT/MRI of abdomen, pelvis, and other areas of known disease at Screening plus any areas of newly suspected disease) should be performed at Screening (within 21 days prior to first dose of study drugs **[Phase 1b] or randomization [Phase 2])** and every 6 weeks ±1 week from the date of ~~enrollment~~ **first dose of study drugs (Phase 1b) or randomization (Phase 2),** or sooner if clinically indicated, until documentation of disease progression. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks, until (1) the start of new anticancer treatment, (2) disease progression (3) death, or (4) the end of the study, or withdrawal of consent, whichever occurs first. Confirmation is not required for best overall response (BOR) of CR or PR in either Phase 1b or Phase 2 parts of the trial.
Footnote w: A bone scan (^{99}m-technetium polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET) to assess bone metastases should be performed within 6 weeks prior to first dose of study drugs and then every 24 weeks ±1 week after the date of the first dose of study drugs, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicates CR has been achieved, a bone scan will be performed within 2 weeks to exclude bone metastases. The same methodology and acquisition techniques used at screening should	**Footnote ~~w~~ x:** A bone scan (^{99}m-technetium ~~polyphosphonate~~ **based** scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET) to assess bone metastases should be performed within 6 weeks prior to first dose of study drugs **(Phase 1b) or randomization (Phase 2)** and then every 24 weeks ±1 week after the date of the first dose of study drugs **(Phase 1b) or randomization (Phase 2)**, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicates CR has been achieved, a bone scan will be performed within 2 weeks to exclude bone metastases. The same

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be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional CT/MRI imaging.	methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional CT/MRI imaging.
Footnote x: A brain scan (CT with contrast or MRI pre- and post- gadolinium) must be performed at Screening (within 21 days prior to first dose of study to assess potential CNS disease and/or metastases. For the duration of the study (ie, post-Baseline), CT/MRI of the brain will be performed if clinically indicated, and within a target of 1 week after a subject achieves a CR. For subjects with history of treated brain metastases, brain scans will be performed at tumor assessment time points if clinically indicated. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability.	Footnote ~~x~~ **y**: A brain scan (CT with contrast or MRI pre- and post- gadolinium) must be performed at Screening (within 21 days prior to first dose of study drugs **[Phase 1b] or randomization [Phase 2])** to assess potential CNS disease and/or metastases. For the duration of the study (ie, post-Baseline), CT/MRI of the brain will be performed if clinically indicated, and within a target of 1 week after a subject achieves a CR. For subjects with history of treated brain metastases, brain scans will be performed at **all** tumor assessment time points ~~if clinically indicated.~~ The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability.
Reason(s) for the Amendment: *Footnote i: Since ECG is being done before and after Eribulin administration use of the word Single at the start was deleted to avoid confusions.* *Other footnotes: To align footnote definitions with changes in the protocol content and other sections.*	

ORIGINAL TEXT	***AMENDED TEXT***
Table 8 Schedule of Procedures and Assessments	***Table 8 Schedule of Procedures and Assessments***
Blood samples for potential PGx, PD (plasma-HA; biomarkers), and safety (ADA) analyses[j]	Two additional rows added**:** **(1) Blood samples for potential PGx[j]** **(2) Blood samples for potential ADA analyses[j]** Revised row: Blood samples for potential ~~PGx,~~ PD (plasma-HA; biomarkers)~~, and safety (ADA) analyses~~[j]
Footnote i: Single 12-lead ECG will be performed at screening, C1 Day 1, C1 Day 8, and as clinically indicated during the study. Electrocardiograms obtained at C1 Day 1 and C1 Day 8 should be performed just prior to and immediately after receiving the eribulin mesylate infusion. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.	Footnote i: ~~Single~~ 12-lead ECG will be performed at screening, C1 Day 1, C1 Day 8, and as clinically indicated during the study. Electrocardiograms obtained at C1 Day 1 and C1 Day 8 should be performed just prior to and immediately after receiving the eribulin mesylate infusion. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

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Footnote J: Blood samples for all **Phase 2/Arm A** subjects will be collected at the PEGPH20 predose on Day -2 or C1 Day -1 for potential pharmacogenomics analyses. Blood samples for potential pharmacodynamic (plasma-HA and biomarkers) and safety (ADA) analyses will be collected at both the PEGPH20 predose on Day -2 or C1 Day -1 and at the End of Treatment Visit, or whenever a subject is withdrawn from study treatment.	Footnote J: Blood samples for all Phase 2/Arm A subjects will be collected at the PEGPH20 predose on Day -2 or C1 Day -1 for potential pharmacogenomics analyses. **Blood samples for potential ADA analyses will be collected at PEGPH20 predose on Day -2 or C1 Day -1 and at the End of Treatment Visit (or whenever a subject is withdrawn from the study). Blood samples for potential pharmacodynamics (PD) for plasma-HA and biomarkers analyses will be collected during screening, at the PEGPH20 predose on Day -2 or C1 Day -1, C1 Day 7, C2 Day -1, Day 1 of every other cycle (C3, C5, C7, etc.),** ~~Blood samples for potential pharmacodynamic (plasma-HA and biomarkers) and safety (ADA) analyses will be collected at both the PEGPH20 predose on Day -2 or C1 Day -1~~ and at the End of Treatment Visit, or whenever a subject is withdrawn from study treatment.
Footnote x: bone scan (^{99}m-technetium polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET) to assess bone metastases should be performed within 6 weeks prior to first dose of study drugs and then every 24 weeks ±1 week after the date of the first dose of study drugs, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicates CR has been achieved, a bone scan will be performed within 2 weeks to exclude bone metastases. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional CT/MRI imaging.	Footnote **x;** A bone scan (^{99}m-technetium ~~polyphosphonate~~ **based** scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET) to assess bone metastases should be performed within 6 weeks prior to first dose of study drugs and then every 24 weeks ±1 week after the date of the first dose of study drugs, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicates CR has been achieved, a bone scan will be performed within 2 weeks to exclude bone metastases. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional CT/MRI imaging.
Reason(s) for the Amendment: *Footnote i: Since ECG is being done before and after Eribulin administration use of the word Single at the start was deleted to avoid confusions.* *Other footnotes: To align footnote definitions with changes in the protocol content and other sections.*	

ORIGINAL TEXT	***AMENDED TEXT***
Table 9 Schedule of Procedures and Assessments	***Table 9 Schedule of Procedures and Assessments***
Blood samples for potential PGx and PD biomarkers) analyses[j]	Blood samples for potential PGx ~~and PD biomarkers) analyses~~[j]
	Revised row: Blood samples for potential ~~PGx and PD~~

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	~~(biomarkers)~~ analyses[j] Added new row: **Blood samples for potential PD (plasma-HA; biomarkers) analyses** [j]
<table><tr><th>Procedures/ Assessments</th><th>Screening</th><th>Baseline[d]</th><th>Treatment Cycle 1</th></tr><tr><td>12-lead ECG[i]</td><td>X</td><td>X</td><td>X</td></tr></table>	<table><tr><th>Procedures/ Assessments</th><th>Screening</th><th>Baseline[d]</th><th>Treatment Cycle 1</th></tr><tr><td>12-lead ECG[i]</td><td>X</td><td>~~X~~</td><td>X</td></tr></table>
Footnote g: At least 5 (preferred 10) unstained, consecutive slides of one archival tumor block or paraffin block, or a fresh tumor biopsy that meet specific tissue sample requirements are required. Any remaining tumor tissues not used for determination of HA level may be used for potential assessment of mutations and other genetic alterations or genes that may be important in the development and progression of cancer as well as for potential use in diagnostic development.	Footnote g: **At least 10** ~~At least 5 (preferred 10)~~ unstained, consecutive slides of one archival tumor block or paraffin block, or a fresh tumor biopsy that meet specific tissue sample requirements are required. Any remaining tumor tissues not used for determination of HA level may be used for potential assessment of mutations and other genetic alterations or genes that may be important in the development and progression of cancer as well as for potential use in diagnostic development.
Footnote i: Single 12-lead ECG will be performed at screening, C1 Day 1 (or Baseline), C1 Day 8, and as clinically indicated during the study. Electrocardiograms obtained at C1 Day 1 and C1 Day 8 should be performed just prior to and immediately after receiving the eribulin mesylate infusion.Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.	Footnote i: ~~Single~~ 12-lead ECG will be performed at screening, C1 Day 1 (~~or Baseline~~), C1 Day 8, and as clinically indicated during the study. Electrocardiograms obtained at C1 Day 1 and C1 Day 8 should be performed just prior to and immediately after receiving the eribulin mesylate infusion. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.
Footnote j: Blood samples for all **Phase 2/Arm B** subjects will be collected at the eribulin mesylate predose on Day -1 or C1 Day 1 for potential pharmacogenomic analyses. Blood samples for potential pharmacodynamics (biomarkers) analyses will be collected at both the eribulin mesylate predose on Day -1 or C1 Day 1 and at the End of Treatment Visit, or whenever a subject is withdrawn from study treatment.	Footnote j: **Blood samples for all Phase 2/Arm B subjects will be collected at the eribulin mesylate predose on Day -1 or C1 Day 1 for potential pharmacogenomics (PGx) analyses. Blood samples for potential pharmacodynamics (PD) for plasma-HA and biomarkers analyses will be collected during screening, at the eribulin mesylate predose on Day -1 or C1 Day 1, C1 Day 8, C2 Day 1, Day 1 of every other cycle (C3, C5, C7, etc.) and at the End of Treatment Visit, or whenever a**

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	subject is withdrawn from study treatment
Footnote t: bone scan (^{99}m-technetium polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET) to assess bone metastases should be performed within 6 weeks prior to first dose of study drugs and then every 24 weeks ±1 week after the date of the first dose of study drugs, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicates CR has been achieved, a bone scan will be performed within 2 weeks to exclude bone metastases. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional CT/MRI imaging	Footnote t: A bone scan (^{99}m-technetium ~~polyphosphonate~~ **based** scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET) to assess bone metastases should be performed within 6 weeks prior to first dose of study drugs and then every 24 weeks ±1 week after the date of the first dose of study drugs, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicates CR has been achieved, a bone scan will be performed within 2 weeks to exclude bone metastases. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional CT/MRI imaging.
Reason(s) for the Amendment: *To align tables with changes in the protocol content and other sections.*	

ORIGINAL TEXT	*AMENDED TEXT*
Appendix 1 Overview of RECIST v1.1 for Evaluation of Tumors Response	**Appendix 1 Overview of RECIST v1.1 for Evaluation of Tumors Response**
Tumor response assessments in this clinical study will use RECIST v1.1 guidelines based on the article by Eisenhauer, et al., 2009, entitled "New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)." This Appendix contains an overview of the RECIST v1.1 guidelines. For complete details, the Eisenhauer article, published in the *European Journal of Cancer*, is available online at: http://www.ejcancer.com/article/S0959-8049(08)00873-3/abstract	Tumor response assessments in this clinical study will use RECIST v1.1 guidelines based on the article by Eisenhauer, et al., 2009, entitled "New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)." **The sole modification to RECIST 1.1 to be implemented in this study is that chest x-rays may not be used to follow disease; only CT scans may be used to follow chest disease. Best overall response of stable disease (SD) requires at least 1 posttreatment assessment that meets the SD criteria ≥5 weeks after the start of treatment.** ~~This Appendix contains an overview of the RECIST v1.1 guidelines.~~ For complete details, the Eisenhauer article, published in the *European Journal of Cancer*, is available online at: http://www.ejcancer.com/article/S0959-8049(08)00873-3/abstract

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Baseline Tumor Assessment Subjects are required to have measurable disease, defined as the presence of at least 1 measurable lesion, to be eligible for entry into the study. Measurable…… ……. **……** The clinical relevance of the duration of SD varies for different tumor types and grades. For this protocol, duration of SD is not being measured.	~~**Baseline Tumor Assessment**~~ ~~Subjects are required to have measurable disease, defined as the presence of at least 1 measurable lesion, to be eligible for entry into the study.~~ ~~Measurable……~~ ~~……~~ ~~**……**~~ ~~The clinical relevance of the duration of SD varies for different tumor types and grades. For this protocol, duration of SD is not being measured.~~
Response Review For this Phase 2 study, response review will be performed at the site by appropriately qualified personnel (radiologist in conjunction with clinical investigator).	~~**Response Review**~~ ~~For this Phase 2 study, response review will be performed at the site by appropriately qualified personnel (radiologist in conjunction with clinical investigator).~~
Reporting of Results All subjects included in the study should be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible.	~~**Reporting of Results**~~ ~~All subjects included in the study should be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible.~~
Reason(s) for the Amendment: *Administrative change*	

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ORIGINAL TEXT	*AMENDED TEXT*
12 Appendices	12 Appendices
	Added Appendix 1 Khorana's risk assessment score

Khorana's risk assessment score.

Patient characteristic		Risk score
Site of primary cancer		
• Very high risk (stomach, pancreas)		2
• High risk (lung, lymphoma, gynecologic, bladder, testicular)		1
Prechemotherapy platelet count 350×10^9/l or higher		1
Hemoglobin level less than 10 g/l or erythropoiesis-stimulating agents		1
Prechemotherapy leukocyte count higher than 11×10^9/l		1
BMI 35 kg/m^2 or higher		1
Total Score	Risk category	Risk of symptomatic VTE
0	Low	0.3–0.8%
1, 2	Intermediate	1.8–2.0%
3 or higher	High	6.7–7.1%

BMI, body mass index; VTE, venous thromboembolism.

Reason(s) for the Amendment:

As a reference for updates to the eligibility criteria

Clinical Study Protocol Amendment

Study Protocol Number: E7389-M000-219

Study Protocol Title: A Randomized, Open-label, Multicenter Phase 1b/2 Study of Eribulin Mesylate in Combination with PEGylated Recombinant Human Hyaluronidase (PEGPH20) versus Eribulin Mesylate Alone in Subjects with Human Epidermal Growth Factor Receptor (HER2)-negative, High-Hyaluronan (HA) Metastatic Breast Cancer (MBC)

Investigational Product Names: E7389/eribulin mesylate and PEGylated recombinant human PH20 hyaluronidase (PEGPH20)

IND Numbers: 113851 (eribulin mesylate), 102770 (PEGPH20)

EudraCT Number 2015-004740

SIGNATURES

Authors:

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03/11/16
Date

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E7389-M000-219 - Protocol Summary of Changes Amendment 01

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Clinical Approval	07-Nov-2016 10:32 GMT-05