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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

VERSION: 1.0

DATE OF PLAN: *25-JULY-2024*

STUDY DRUG: *UNESBULIN*

PROTOCOL NUMBER:

PTC596-ONC-008-LMS

STUDY TITLE:

A PHASE 2/3 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF UNESBULIN IN UNRESECTABLE OR METASTATIC, RELAPSED OR REFRACTORY LEIOMYOSARCOMA

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Abbreviation or Specialized Term	Explanation
AE	adverse event
AIC	5-amino-imidazole-4-carboxamide
BIW	twice weekly
BOR	best overall response
BSA	body surface area
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CSR	clinical study report
DCR	disease control rate
DOR	duration of response
DTIC	dacarbazine
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
HR	hazard ratio
ICR	independent central review
ITT	Intent-to-Treat
KM	Kaplan-Meier
LMS	leiomyosarcoma
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
ORR	objective response rate
OS	overall survival
PD	disease progression
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PRO	patient-reported outcomes
PS	performance status
PT	preferred term
Q21D	once every 21 days
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION AND OVERVIEW

The purpose of this statistical analysis plan (SAP) is to describe the procedures and statistical methodology to be implemented for data analysis of the study described in protocol PTC596-ONC-008-LMS (Global Version 4.0; 28 November 2023). It also covers any later amendments to the protocol that may be produced that have no material effect on the statistical analysis (refer to relevant file note(s), if applicable). However, if circumstances arise during the study such that more appropriate analysis procedures or methodologies become available/are warranted, or if there is a protocol amendment which necessitates changes to the SAP, then this document will be revised. Any deviations from the SAP will be substantiated by sound rationale and will be documented in the clinical study report (CSR). Otherwise, the CSR will consider all the information defined in this SAP.

Table, figure, and listing specifications are contained in a separate document.

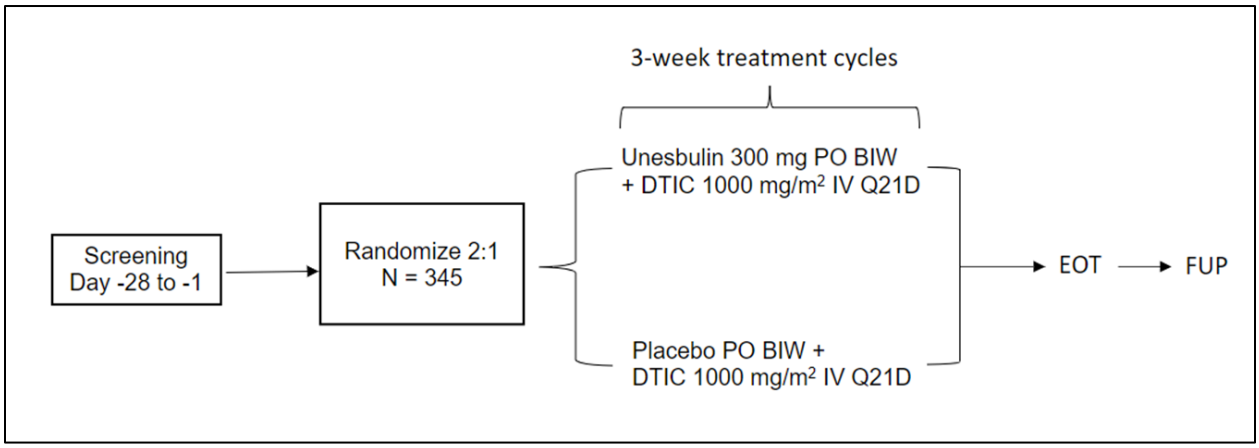
1.1. Study Design

This is an international, multicenter, randomized, double-blind, placebo-controlled, Phase 2/3 study to compare the efficacy and safety of unesbulin plus dacarbazine (DTIC) versus placebo plus DTIC in subjects with unresectable or metastatic, relapsed or refractory leiomyosarcoma (LMS) who have received at least 1 prior line of systemic therapy.

Eligible subjects will be randomized 2:1 (unesbulin plus DTIC: placebo plus DTIC) to one of the following treatment groups as shown in Figure 1:

- **Unesbulin plus DTIC**: Unesbulin 300 mg will be administered PO twice weekly (BIW) in each 3-week treatment cycle. DTIC 1000 mg/m^2 will be administered IV once every 21 days (Q21D).
- **Placebo plus DTIC**: Matching placebo will be administered PO BIW in each 3-week treatment cycle. DTIC 1000 mg/m^2 will be administered IV Q21D.

Figure 1: Study Design



Abbreviations: AE, adverse event; BIW, twice weekly; DTIC, dacarbazine; EOT, end-of-treatment; FUP, follow-up; OS, overall survival; Q21D, once every 21 days
Note: All subjects will receive treatment until evidence of disease progression, unacceptable toxicity, or other withdrawal criteria are met. An EOT assessment will be performed within 30 days after the end of treatment or until recovery or stabilization of the AE, whichever occurs latest. For subjects requiring immediate initiation of a new treatment option, an EOT visit may be completed earlier. A safety FUP assessment should be performed by phone at

30 days (±3 days) after the EOT. Survival FUP assessments will occur by phone every 3 months (±7 days) after the EOT visit until the later of 184 events or 2 years after the last subject is randomized.

For approximately 300 subjects with 1 to 3 prior lines of treatment, randomization will be stratified as follows:

- Number of prior systemic therapies (1 or >1)
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) score (0 or 1)
- Histological tumor type (uterine versus nonuterine LMS)

Forty-five subjects with at least 4 prior lines of treatment will be randomized and stratified as follows:

- ECOG PS score (0 or 1)
- Histological tumor type (uterine versus nonuterine LMS)

1.2. Study Objectives and Endpoints

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective: PFS of unesbulin plus DTIC versus placebo plus DTIC	**Primary Endpoint**: PFS per RECIST 1.1 assessed by an independent central imaging laboratory.
Key Secondary Objective: Efficacy: OS of subjects treated with unesbulin plus DTIC versus placebo plus DTIC	**Key Secondary Endpoint**: Efficacy: OS
Other Secondary Objectives: Efficacy: Antitumor activity of unesbulin plus DTIC versus placebo plus DTIC Safety: Safety and tolerability of unesbulin plus DTIC versus placebo plus DTIC	**Other Secondary Endpoints:** Efficacy: • ORR (proportion of subjects with BOR of either CR or PR) • DCR or CBR, defined as the proportion of subjects with BOR of CR, PR, or at least 3 months of SD • DoR Safety: Vital signs, physical examination, ECG, laboratory abnormalities, ECOG PS scores, and AEs
Exploratory Objectives: Efficacy: Evaluate the antitumor activity of unesbulin plus DTIC versus placebo plus DTIC in subjects with at least 4 prior lines of treatment. PK: • Evaluate the PK of unesbulin in the presence of DTIC in subjects with LMS • Evaluate the PK of DTIC/AIC alone and in the presence of unesbulin in subjects with LMS.	**Exploratory Endpoints**: Efficacy: PFS, OS, ORR, DCR, and DoR in subjects with at least 4 prior lines of treatment. PK: • PK parameters of unesbulin in subjects who receive unesbulin plus DTIC: C_{max}, T_{max}, and AUC_{0-t} • PK parameters of DTIC and its inactive metabolite AIC in subjects who receive

Objectives	Endpoints
	unesbulin plus DTIC and placebo plus DTIC: Cmax, Tmax, and AUC_{0-t}.
PROs: Compare the effect of unesbulin plus DTIC versus placebo plus DTIC on PROs, including HRQoL assessments.	PROs: 30-item score EORTC QLQ-C30 and EQ-5D-5L
Biomarkers: Measure genotype of subject tumors, assessed by blood sampling, at baseline and posttreatment	Biomarkers: Genetic evaluation of the tumors by analyzing ccfDNA

Abbreviations: AE, adverse event; AIC, 5-amino-imidazole-4-carboxamide; AUC_{0-t}, area under the concentration versus time curve from time zero to the last sampled time or the last non-zero concentration; BOR, best overall response; ccfDNA, circulating cell-free tumor DNA; CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; DoR, duration of response; DTIC, dacarbazine; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire; EQ-5D-5L, EuroQol 5-level EQ-5D version; HRQoL, health-related quality-of-life; ORR, objective response rate; LMS, leiomyosarcoma; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; PROs, patient-reported outcomes; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

1.3. Sample Size

The target sample size is approximately 345 (300 subjects with 1 to 3 prior lines of systemic therapy for the primary analysis and 45 subjects with at least 4 prior lines of systemic therapy for the exploratory analysis).

The sample size was computed based on the comparison of progression-free survival (PFS) between subjects randomized to unesbulin plus DTIC and subjects randomized to placebo plus DTIC. Full details of the sample size assumptions are provided in the study protocol.

1.4. Randomization

Subjects will be randomized 2:1 to either unesbulin plus DTIC or placebo plus DTIC using a central randomization system. For subjects with 1 to 3 prior lines of treatment, randomization will be stratified by the number of prior systemic therapies (1 or >1), ECOG PS score (0 or 1), and histological tumor type (uterine or nonuterine LMS). For subjects with at least 4 prior lines of treatment, randomization will be stratified by ECOG PS score (0 or 1) and histological tumor type (uterine or nonuterine LMS).

1.5. Assessment of Efficacy

Response assessments will be performed by radiological imaging using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria every 6 weeks (±7 days) until disease progression. After Cycle 8, scans are to be performed every 9 weeks. If any subject responds with a complete response (CR) or partial response (PR) at any assessment, then the subsequent confirmatory scan should be performed 4 weeks after the previous scan where the objective response was first evidenced. Assessment of response and the primary endpoint, PFS, will be assessed by an independent central review (ICR) who will be blinded to treatment assignment.

Subjects should be followed with the same imaging procedure throughout the study. Computed tomography scans or magnetic resonance imaging may be used as clinically indicated. If the

subject withdraws for reasons other than tumor progression, an EOT scan should be performed if the last scan was ≥3 weeks earlier.

2. ANALYSIS SETS

2.1. Intent-to-Treat (ITT) Set

The ITT set will include all randomized subjects. Subjects will be grouped based on the group they are randomized to. If a subject receives treatment in the group different from the one to which he/she was randomized, the subject's efficacy data will be analyzed "as randomized." The ITT population will be used as sensitivity analysis for all efficacy analysis.

2.2. Modified Intent-to-treat (mITT) Set

The mITT set will include randomized subjects with 1 to 3 prior lines of therapy. The mITT population will be used in all the efficacy analysis, including analyses of the primary and secondary endpoints. Subjects will be grouped based on the group they are randomized to. If a subject receives treatment in the group different from the one to which he/she was randomized, the subject's efficacy data will be analyzed "as randomized." The mITT Analysis Set is the primary analysis population for this study.

2.3. Safety Analysis Set

The safety analysis set will include all subjects who received at least one dose of study drug (unesbulin/placebo or DTIC). If a subject receives treatment in the group different from the one to which he/she was randomized, the subject's safety data will be analyzed "as treated." The safety analysis set will be used in the statistical analyses for safety.

2.4. Pharmacokinetic Analysis (PK) Set

The PK analysis set will include subjects in the safety analysis set who have at least one measurable plasma concentration of unesbulin, DTIC, or AIC.

3. GENERAL CONSIDERATIONS

3.1. General Considerations

Continuous data will be summarized using number of observations (n), arithmetic mean (mean), standard deviation, median, minimum value (min) and maximum value (max) by treatment group. Categorical variables will be summarized using the frequency count (n) and percentage (%) by treatment group. An overall/total group (i.e., sum of all treatment groups) will generally be presented additionally for summaries of disposition, demography, and baseline characteristics.

For all percentage calculations, the denominator will be the number of subjects in the analysis set for the treatment group, unless otherwise stated.

Only data from protocol scheduled visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables but will be included in the by-subject listings. Descriptive summaries by visit and treatment will be provided for all the primary and secondary efficacy endpoints.

3.2. Estimands

3.2.1. Estimand for Primary Efficacy Analysis (PFS)

Research Question: How does progression free survival time compare between subjects treated with unesbulin (PTC596) in combination with DTIC to those treated with DTIC alone (placebo + DTIC) in the population of subjects with unresectable or metastatic, relapsed or refractory LMS?

Subject Population: Subjects previously treated with 1 to 3 prior lines of systemic therapy, who are randomized to a treatment assignment (unesbulin+DTIC or placebo+DTIC) and further described in the protocol inclusion exclusion criteria.

Endpoint variable: Time from randomization to disease progression or Death due to any cause (whichever occurs first) with disease progression determined according to the RECIST 1.1 and assessed by ICR.

Population-level summary: The hazard ratio (HR) and 95% confidence interval (CI) between unesbulin and placebo

Treatment Condition: unesbulin+DTIC vs. placebo+DTIC

Intercurrent Event Strategy:

a) Discontinuation of DTIC – Treatment Policy
b) Discontinuation of unesbulin – While on treatment
c) Start of subsequent anticancer treatment: While on treatment

3.2.2. Estimand for Overall Survival (OS)

Research Question: How does survival time compare between unesbulin treatment versus placebo in the population of subjects with unresectable or metastatic, relapsed or refractory LMS?

Subject Population: Subjects previously treated with 1 to 3 prior lines of systemic therapy, who are randomized to a treatment assignment (unesbulin+DTIC or placebo+DTIC) and further described the protocol inclusion exclusion criteria.

Endpoint variable: Time from randomization to death.

Population-level summary: The HR and 95% CI between unesbulin and placebo.

Treatment Condition: unesbulin+DTIC vs. placebo+DTIC

Intercurrent Event Strategy:

a) Discontinuation of unesbulin – Treatment Policy
b) Discontinuation of DTIC – Treatment Policy
c) Start of subsequent anticancer treatment: Treatment Policy

3.2.3. Estimand for Objective Response Rate (ORR)

Research Question: How does tumor shrinkage (response) compare between unesbulin treatment versus placebo in the population of subjects with unresectable or metastatic, relapsed or refractory LMS as defined by the study's inclusion exclusion criteria?

Subject Population: Subjects previously treated with 1 to 3 prior lines of systemic therapy, who are randomized to a treatment assignment (unesbulin+DTIC or placebo+DTIC) and further described the protocol inclusion exclusion criteria.

Endpoint variable: Objective response (best overall response [BOR] of CR or PR) per RECIST 1.1 assessed by ICR.

Population-level summary: Proportion and Clopper Pearson 95% CI

Treatment Condition: unesbulin+DTIC vs. placebo+DTIC

Intercurrent Event Strategy:

a) Discontinuation of unesbulin – While on treatment
b) Discontinuation of DTIC – Treatment Policy
c) Start of subsequent anticancer treatment – While on treatment

3.2.4. Estimand for Duration of Response (DOR)

Research Question: What is the difference between subjects treated with unesbulin + DTIC to those treated with placebo+DTIC in the DOR, defined as time from first disease response to disease progression or death (whichever occurs first)?

Subject Population: Subjects previously treated with 1 to 3 prior lines of systemic therapy, who are randomized to a treatment assignment (unesbulin+DTIC or placebo+DTIC) and have tumor response.

Endpoint variable: Objective response per RECIST 1.1 assessed by ICR.

Population-level summary: Median and 95% CI

Treatment Condition: unesbulin+DTIC vs. placebo+DTIC

Intercurrent Event Strategy:

a) Discontinuation of unesbulin – While on treatment
b) Discontinuation of DTIC – Treatment Policy
c) Start of subsequent anticancer treatment – While on treatment
d) Disease response (objective response rate [ORR]) - Principal stratum

3.3. Multiplicity

A hierarchical (fixed sequence) testing procedure will be applied in the mITT analysis set. If the primary endpoint is significant at the 0.025 level (1-sided), then the key secondary endpoint (OS) will be tested in sequence. Additionally, tests for the secondary endpoints will be performed in sequence.

For the interim analysis of the primary endpoint (PFS), alpha allocation will be controlled for the key secondary endpoint OS as a separate group sequential design and monitoring will be performed at the interim and the final analysis timepoints by using the Lan-DeMets spending function that approximates the O'Brien-Fleming approach. The family-wise significance level is 0.025, with 0.000184 allocated at the interim analysis.

3.4. Missing Data

For the primary analysis of PFS only observed disease response data will be used. Data for subjects without progression or without any scans will be censored as described in Table 3.

3.5. Interim Analysis

One interim analysis of the study's primary endpoint (PFS) was planned to be performed when approximately 36% of the PFS events occur (approximately 88 events). An O'Brien-Fleming spending function will be used to calculate the sequential HR boundaries based on the actual number of PFS events.

Assuming there are 88 events at this interim analysis, then the study may stop for efficacy if the observed HR is less than 0.447 or stop for futility if the observed HR is more than 0.67.

Based on the results of planned interim analysis, the Data Monitoring Committee recommended discontinuing the study due to futility.

3.6. Data Definitions and Analysis Issues

3.6.1. Baseline Definition

The Randomization Visit will be defined as Day 1 of the study. For all endpoints, unless otherwise specified, the baseline value will be the latest pre-randomization assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

For the purposes of calculating summary statistics of the outcome measures, change from baseline will be derived as follows:

- Change from baseline = post-baseline value – baseline value

3.6.2. Multicenter Studies

Due to the large number of participating sites resulting in diminished sample sizes within each site, no adjustment or stratification for site will be performed. Data from all centers will be pooled for the primary analysis. By site/region analysis of the primary endpoint may be explored.

3.7. Changes to Protocol Specified Analysis

There are no changes in the protocol-specified analyses of efficacy (primary, secondary, and exploratory), safety, and PK endpoints. Exploratory analyses for the patient-reported outcomes and biomarkers will not be performed due to futility of the primary efficacy endpoint.

4. PATIENT DATA

4.1. Patient Disposition

The following subject disposition information will be provided:

- Number of screenings.
- Number of unique subjects screened.
- Number of subjects in the ITT, mITT, and safety analysis set
- Number who have discontinued treatment.
- The primary reason for treatment discontinuation

A listing of these data will also be provided.

4.2. Data Sets Analyzed

A summary of the number of subjects for each analysis dataset will be provided.

4.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics including age, age group (18-64 years, 65-84 years, 85 years and over), sex, race, ethnicity, height, weight, body surface area (BSA), body mass index, region, and time since initial diagnosis will be summarized by treatment group and overall, for the safety analysis set. Stratification factors (prior lines of therapy, ECOG, histological tumor type) will also be summarized.

4.4. Disease Characteristics

Disease characteristics include histological tumor type (see above), measurable disease status per RECIST 1.1 criteria, disease stage at study entry, and time from initial diagnosis.

Demographic and baseline characteristic data, including disease characteristics, will be listed by subject.

4.5. Medical History

Subject medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 25 or higher) coding dictionary. A summary table by system organ class (SOC) and preferred term (PT) will be provided for each treatment group and overall. Subject medical history data will be listed by subject.

4.6. Protocol Deviations

Before database lock, protocol deviations will be documented separately in a stand-alone document that includes deviation category (e.g., violation of inclusion and exclusion criteria at screening, use of excluded concomitant medications, received the wrong treatment or incorrect dose), deviation description, CSR/non-CSR reportable, and visit/time point for each deviation).

CSR-reportable protocol deviations include those related to inclusion/exclusion criteria, conduct of the trial, subject management or subject assessment that impact the safety of the subjects or

jeopardize the quality of the study data. CSR-reportable protocol deviations are equivalent to a major protocol deviation.

CSR-reportable protocol deviations will be summarized. A subject listing of CSR-reportable protocol deviations will be provided for the safety analysis set.

4.7. Prior and Concomitant Medications

All investigator terms for medications recorded on the electronic case report form (eCRF) will be coded using the World Health Organization Drug Dictionary (version WHODrug-Global-B3 Sep 2021 or later).

Prior medications will be defined as medications started prior to the first dose of study drug. Concomitant medications will be defined as medications (other than the study drug) that either (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose and within 30 days after last dose of study drug. Any medication started before the first dose of study drug and continued at the time of first dose will be considered as both prior and concomitant.

Any medication with partial or missing start date in which the prior medication status cannot be determined will be considered as a prior medication. Similarly, any medication with partial or missing end date in which the concomitant medication status cannot be determined will be considered as a concomitant medication.

Prior medication and concomitant medication will be summarized by treatment group as following for safety analysis set as:

- Number and percentage of subjects with at least one prior/concomitant medication.

By Anatomical Therapeutic Chemical level 2 and PT.

A subject data listing of all prior and concomitant medications will be provided.

Table 2: Study Phases for Concomitant Medications

Study Phase	Definition
Prior	End date < Study treatment start date
Prior and concomitant	Start date < Study treatment start date and were continuing at the time of the first dose of study drug
Post-treatment	Start date > Study treatment stop date + 30 days
Concomitant	If the medication is not prior nor post-treatment

4.8. Extent of Exposure

The following will be summarized: duration of exposure for unesbulin/placebo and DTIC, number of unesbulin/placebo cycles completed, and number of unesbulin/placebo doses received.

Duration of exposure (days) is defined as

Last dose date (unesbulin/placebo) - First dose date + 1.

For unesbulin/placebo, last dose date is the dose date that recorded in the diary eCRF and/or End of treatment eCRF. Subjects known to be still on treatment after the data cut-off date will have the last dose date imputed as the data cut-off date.

The same calculation will be used to compute the duration of DTIC exposure. For DTIC, the last dose date is the dose date recorded in the DTIC administration eCRF and/or End of treatment eCRF. Subjects known to be still on treatment after the data cut-off date will have the last dose date imputed as the data cut-off date.

Duration of exposure and number of doses will be summarized by treatment group and overall for the safety analysis set.

By-subject listings will also be provided.

4.9. Treatment Modifications

The following will be summarized by treatment group for unesbulin/placebo and DTIC.

- Number of subjects with missed doses / reasons of missed doses
- Number of subjects with reduced doses / reasons for dose reductions.
- Infusion interruptions (DTIC) / reasons for infusion interruptions

A by-subject listing will also be provided.

5. EFFICACY ANALYSIS

The efficacy endpoint will be analyzed.

- PFS per ICR

Other efficacy endpoints (listed below) will be analyzed.

- OS
- ORR
- Disease control rate (DCR) or clinical benefit rate (CBR)
- Duration of response (DOR)

Tabular summaries for efficacy endpoints will be provided for the following analysis populations:

- The mITT population (the primary analysis population),
- The ITT population (sensitivity analysis)
- Subset of the ITT population with 4 or more prior line therapy (sensitivity analysis)
- By histological tumor type (Uterine and non-uterine) for the mITT population (subgroup analysis)
- Baseline ECOG PS score (0 and 1) for the mITT population (subgroup analysis)
- Prior lines of therapy (1 and >1) for the mITT population (subgroup analysis)
- Prior lines of therapy (4 or more) for the non-mITT population (subgroup analysis)
- Histologic tumor type in combination with number of prior lines of therapy (uterine with 1 prior line; uterine with 2-3 prior lines, non-uterine with 1 prior line; non-uterine with 2-3 prior lines) for the mITT population (subgroup analysis)

By-subject listings will also be provided.

5.1. Primary Analyses

5.1.1. Progression Free Survival (PFS)

PFS will be analyzed twice during the study: at the interim analysis, when approximately 88 events have occurred and at final analysis after 245 events have occurred. PFS is defined as the time from randomization to documented disease progression or death due from any cause, whichever occurs first. Subjects who are alive and have not progressed at the time of the analysis will be censored at the time of their last tumor assessment that was a CR, PR, SD, or non-CR/non-PD. Details of the censoring scheme for this endpoint are described in Table 3.

PFS will be analyzed using Kaplan-Meier (KM) methods. A summary table of the number of events, the number of censors, and KM estimates (25th, 50th, 75th percentile of PFS along with the 95% CI, and PFS probability at 2, 4, 6, 8 months, respectively) will be provided by treatment.

KM curve of PFS will be provided using the mITT and ITT populations.

The HR, p-value and 95% CI will be estimated using a stratified Cox proportional hazards regression model controlling for study stratification factors include prior lines of therapy (1 versus

>1), ECOG PS score (0 versus 1), and LMS origin (uterine versus nonuterine). If there are stratification errors (eg, a subject with ECOG score=1 randomized in the ECOG score=0), this analysis will be stratified by the planned strata in the study randomization scheme (ie, stratification errors will be ignored). However, a sensitivity analysis with PFS stratified by actual strata will be performed. A listing showing planned and actual randomization strata will also be provided. Strata with less than 5 subjects in any given treatment arm will not be included (ie, when there are less than 5 subjects in the ECOG =1 for the placebo group then ECOG stratum will be eliminated from the model).

Table 3: Censoring and Event Scheme for PFS

Scenario	Date of Event/Censoring	Outcome
No post-baseline response assessments and no death or PD	Date of randomization	Censored
No PD and no death	Date of last adequate response assessment	Censored
New anti-cancer treatment started before first PD	Date of last adequate response assessment prior to date of new anticancer treatment	Censored
New anticancer treatment taken but did not have PD/Death.	Date of last adequate response assessment prior to date of new anticancer treatment	Censored
New anti-cancer treatment taken after treatment starts but prior to the first response assessment	Date of randomization	Censored
PD	Date of PD If PD occurred within the timeframe of 2 consecutive scheduled scans[a] from the last adequate response assessment	Progressed
	Date of last adequate response assessment If the date of PD occurred after missing more than 2 consecutive scheduled scan assessments[a]	Censored
Death	Death date If death occurred within the timeframe of 2 consecutive scheduled scans[a] from the last adequate response assessment.	Progressed
	Death date If there are no post-baseline response assessments and death occurred within ≤14 weeks of the randomization date.	Progressed
	Date of randomization If there are no post-baseline response assessments and death occurred >14 weeks from the first dose.	Censored
	Date of last adequate response assessment If the date of death occurred after missing more than 2 consecutive scheduled scan assessments[a]	Censored

Abbreviations: PD, disease progression.

[a] 2 consecutive scheduled scan assessments are defined in weeks as follows:
> 14 weeks (6+1+6+1=14) post last tumor assessment, if PD/death occurred within first 8 cycles (24 weeks) of treatment
> 17 weeks (6+1+9+1=17) post last tumor assessment, if subjects' PD/death occurs between cycle 8 and 14 (42 weeks) of treatment
> 20 weeks (9+1+9+1=20) post last tumor assessment, if subjects' PD/death occurs after cycle 14 (42 weeks) of treatment

The last adequate response assessment is defined as the date subject had an overall response of (CR, PR or SD or non-CR/non-PD)

5.1.2. Sensitivity Analysis for PFS

The following sensitivity analyses will be performed for the primary endpoint.

a. A sensitivity analysis to determine the effect of any stratification errors during the study randomization, for example the randomization of a subject with 1 prior line of therapy, occurring in the stratum of subjects with >1 prior line.
The primary PFS analysis described in Section 5.1.1 will be re-run with the stratification variables based on actual strata. This analysis will be performed with the mITT population redefined by the actual number of prior lines of therapy.

b. The PFS analysis described in Section 5.1.1 will be re-run including all randomized subjects (ITT population). For this analysis, the number of prior lines of therapy will be stratified using the following levels: 1, 2-3, >3.

c. The PFS analysis described in Section 5.1.1 will be re-run restricted the mature cohort of subjects, defined as subjects in the mITT population, who have had an opportunity to complete 6 months of follow-up (time from randomization until the data-cut date is ≥ 6months).

d. The PFS analysis described in Section 5.1.1 will be re-run restricted to subjects who received "adequate treatment exposure", defined as subjects who received at least 50% of 2 cycles of treatment with unesbulin/placebo (ie, 6 doses), received at least 2 doses of DTIC, and had a baseline and at least 1 postbaseline response assessment using RECIST Version 1.1 criteria; or subjects who died prior to Cycle 3 Day 1 and received at least 1 dose of unesbulin.

5.1.3. Subgroup Analyses for PFS

The primary endpoint will be evaluated for the following subgroups.

- By histological tumor type (uterine and non-uterine) for the mITT population
- Baseline ECOG PS score (0 and 1) for the mITT population
- Prior lines of therapy 1, 2, and 3 (EDC data) for the mITT population
- Prior lines of therapy (4 or more) for the non-mITT population
- Histologic tumor type in combination with number of prior lines of therapy (uterine with 1, 2 and 3 prior lines, non-uterine with 1, 2 and 3 prior lines (EDC data) for the mITT population

5.2. Key Secondary Analyses

5.2.1. Overall Survival

Overall survival (OS) is defined as the time in months from the randomization date to the date of death from any cause or date last known alive for those who did not die.

Specifically,

OS = Date of death or date last known alive – Date of first dose + 1

Subjects will be censored at the last date they are known to be alive. The last known alive date will be the last date of any subject record in the study database. The date may be the last visit date or last contact date that the subject is known to be alive. Subjects who only have baseline record will be censored at the first dose date.

OS will be analyzed using KM methods. A summary table of the number of deaths, the number of censors, and KM estimates (25th, 50th, 75th percentile of OS along with the 95% CI, and OS probability at 3, 6, 9, 12 months, respectively) will be provided by treatment group using the mITT population.

KM curve of OS will be provided using the mITT population.

5.3. Secondary Analyses

5.3.1. Tumor Response

Tumor response includes the BOR, ORR, DCR (or CBR) and DOR. Tumor response endpoints will be summarized for the mITT population, ITT population, and randomized subjects with 4 or more prior lines of therapy. The analysis will be based on ICR scans per to RECIST v 1.1. Results based on investigator assessment will also be provided. A by subject listing of tumor response data will be provided.

5.3.1.1. Best Overall Response

BOR is defined as the best response designation recorded between randomization date and the date of objectively documented progression per RECIST 1.1 or the date of initiation of subsequent therapy or palliative local therapy, whichever occurs first. For subjects without documented progression or subsequent therapy or palliative local therapy, all available response designations will contribute to the BOR determination. For this study responses of CR or PR require confirmation by a subsequent assessment that is performed a minimum of 4 weeks or later from when the initial response is observed. Table 4 illustrates how CR or PR responses will be confirmed.

BOR will be summarized using counts and percentages by treatment group, this analysis will be based on subjects with measurable diseases with at least 1 post-randomization assessment.

Table 4: Confirmed Response Based on Subsequent Assessment

First Time Point Response[a]	Second Time Point Response	Confirmed Response (Best Response)[b]
PD	No further evaluation	PD
NE	PD	PD
CR	PD	SD or PD[c]
PR	PD	SD or PD[c]
SD	PD	SD or PD[c]
CR	CR	CR
CR	NE[a]	SD or NE[d]
PR	CR	PR
PR	PR	PR

First Time Point Response[a]	Second Time Point Response	Confirmed Response (Best Response)[b]
PR	SD[ae]	SD
PR	NE[a]	SD or NE[d]
SD	CR	SD
SD	PR	SD
SD	SD	SD
SD	NE	SD or NE[d]
NE	CR	SD
NE	PR	SD
NE	SD	SD
NE	NE	NE

Abbreviations: CR, complete response; NE, not evaluable; PD, disease progression; PR, partial response; SD, stable disease.

[a] Subsequent documentation of CR may provide confirmation of a previously identified CR for subjects where the second integrated response was NE. Subsequent documentation of PR may provide confirmation of a previously identified PR for subjects where the second integrated response was NE or SD. If the third TPR confirms the CR (or PR) then the Confirmed Response will be CR (or PR). For this study, only one (1) intervening NE is allowed between CRs/PRs. For example: CR NE CR = CR; PR NE PR = PR. Additionally, one (1) SD is allowed between PRs (e.g., PR SD PR = PR).

[b] A Best Response of SD can only be made after the subject is on-study for a minimum of 35 days. If the subject is on study less than 35 days, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

[c] Best response will be SD if the first TPR is after 35 days on study. Otherwise, the best response will be PD.

[d] Best response will be SD if the first TPR is after 35 days on study. Otherwise, the best response will be NE.

[e] TPR is SD if the increase from the first to the second assessment does not qualify for PD.

5.3.1.2. Objective Response Rate (ORR)

Objective response is defined as achieving a confirmed BOR of CR or PR per RECIST 1.1. ORR is defined as the proportion of subjects with objective response. The proportion of subjects with ORR and corresponding two-sided exact Clopper Pearson binomial 95% CIs will be provided by treatment group for both the ICR-assessed scans and investigator-assessed scans. Additionally, the difference between treatment arms and Wald 95% CI for the difference will be provided.

5.3.1.3. Disease Control Rate (or) Clinical Benefit Rate.

For this study, disease control (or clinical benefit) is defined as achieving a confirmed BOR of CR, PR, or at least 3 months of SD. The proportion of subjects who achieve disease control and corresponding two-sided exact Clopper Pearson binomial 95% CI will be estimated for both the ICR and investigator assessments. In addition, the difference between the groups and Wald 95% CI for the difference will also be provided.

5.3.1.4. Duration of Response

DOR will be only calculated for subjects who have a confirmed response of CR or PR by independent radiology reviews.

DOR is calculated as the earliest documented date of CR or PR to the first date of documented PD or death due to any cause. For subjects without PD or death will be censored at the date of the last evaluable response assessment date. The same censoring rules outlined in Table 3 will be applied to DOR with date of randomization date replaced with the date of first response.

KM estimates (25th, 50th, 75th percentile of DOR along with the 95% CI) will be provided by the treatment group.

5.3.2. Subgroup Analyses for ORR, DCR and DOR

The secondary endpoint will be evaluated for the following subgroups.

- By histological tumor type (uterine and non-uterine) for the mITT population
- Baseline ECOG PS score (0 and 1) for the mITT population
- Prior lines of therapy (1 and >1) for the mITT population
- Prior lines of therapy (4 or more) for the non-mITT population
- Histologic tumor type in combination with number of prior lines of therapy (uterine with 1 prior line; uterine with 2-3 prior lines, non-uterine with 1 prior line; non-uterine with 2-3 prior lines) for the mITT population

6. SAFETY ANALYSES

Safety analyses will be based on safety analysis set unless otherwise specified. subjects in the safety analysis set will be analyzed according to the treatment (actually) received.

6.1. Adverse Events

The adverse event (AE) verbatim descriptions (investigator terms from the eCRF) will be classified into medical terminology using MedDRA. AEs will be coded by SOC and PT using MedDRA, Version 25.0 or later.

An AE will be defined as treatment emergent if one of the following criteria is met:

- A new AE has an onset date on or after the date that study drug (unesbulin/placebo or DTIC) is first administered up-through 30 days after the last dose of study drug.
- A pre-existing AE worsens in severity on or after the date that study drug is first administered through 30 days after the last dose of study drug.

Only treatment-emergent adverse events (TEAEs) will be included in the summary tables.

AEs with missing or partial onset date, such that it cannot be determined if the event occurred prior to the first dose of study, will be counted as TEAE.

Overall summary of TEAE table, will include number and percentage of subjects with any TEAEs, serious AEs, non-serious adverse events (non-SAEs), unesbulin/placebo-related TEAEs, DTIC-related TEAEs, TEAEs leading to unesbulin/placebo withdrawn, TEAEs leading to DTIC withdrawn and TEAEs by highest severity, will be provided by treatment group and overall.

All TEAEs will be summarized by MedDRA SOC and PT. If a subject experiences multiple AEs under the same SOC, the subject will be only counted once for the SOC with the greatest severity. Similarly, if a subject experiences multiple AEs under the same PT and SOC, the subject will be counted only once for the PT with the greatest severity. The table will be sorted by the descending order of the frequency of SOC then by the descending order of the frequency of PT under SOC based on the overall column.

In addition, the following summary tables will be provided:

- All TEAE by PT
- SAE by SOC and PT
- Non-SAE by PT
- SAE and non-SAE occurrence of each PT
- Non-SAE: subjects and occurrence for each PT by reporting threshold 5%
- Unesbulin/placebo-related TEAE by SOC and PT
- DTIC-related TEAE by SOC and PT
- TEAE leading to treatment (unesbulin/placebo or DTIC) discontinuation by SOC and PT
- TEAE leading to study discontinuation by SOC and PT

- All TEAE by maximum severity under each SOC and PT
- All TEAE with at least one Grade 3 or higher by PT

All TEAEs will be listed. In addition, subjects with death, SAE, or AE leading to discontinuation of study treatment during the study will be presented in three separate listings.

6.2. Laboratory Values

Laboratory values will be presented in standard units. For multiple values for a test at a visit from the same laboratory, the last non-missing value at that visit will be used.

Mean and mean change from baseline in clinical laboratory data will be summarized at each scheduled nominal visit by treatment group.

In addition, box plot of hematology and chemistry parameters will be presented by nominal visit and treatment group.

6.3. Physical Examination and Vital Signs

Physical examination will be summarized by nominal visit, and abnormal findings will be listed.

Vital signs (including systolic and diastolic blood pressure, respiratory rate, temperature, heart rate, weight, height, and BSA) will be summarized and presented as actual value and change from baseline at each scheduled nominal visit by treatment group. The number of non-missing values, mean, standard deviation, median, and range (minimum and maximum) will be presented. Change from baseline will be calculated as the postbaseline measurement minus the baseline measurement. If either the baseline or postbaseline value is missing, the observation will not be included in the change from baseline summary. The body temperature will be collected in °F or °C, but reported in °C. Weight will be collected in pounds (lb) or kilograms (kg) but reported in kg.

A listing of all vital sign assessments will be presented for the safety analysis set.

6.4. ECOG Performance Status

ECOG performance status (PS) will be summarized at baseline and shift from baseline to worst level during the treatment phase. A supporting list will also be provided.

6.5. Electrocardiogram (ECG)

ECG parameters (PR, RR, QRS, QT, QTcF, QTcB) and heart rate (HR) actual value and change from baseline will be summarized by treatment group and the overall population. Each subject's triplicate measurements will be averaged at a given time point before the summary. The number of non-missing values, mean, standard deviation, median, and range (minimum and maximum) will be presented. Change will be calculated as the post baseline measurement minus the baseline measurement. If either the baseline or postbaseline value is missing, the observation will not be included in the change from baseline summary.

In addition, a categorical analysis of QTc intervals will be performed for each time point.

The number and percentage of subjects in each QTc interval (<450 msec, 450-480 msec, 481-500 msec, >500 msec) will be summarized at baseline and each of the subsequent time points.

Categories of changes from baseline (≥30 msec and ≥60 msec), maximum QTc intervals at all post dose time points, and maximum changes from baseline will be summarized by visit.

ECG results (PR, RR, QRS, QT, QTcF, QTcB, and classification of Normality, Abnormality with Clinical Significance, or Abnormality without Clinical Significance) will be presented in data listings.

6.6. Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. Pregnancy information will be produced as a listing.

7. EXPLORATORY ANALYSES

7.1. Pharmacokinetics

PK analysis will be described in a separate PK Analysis Plan.

8. MOCK TABLES, LISTINGS, AND GRAPHS

The study tables, listings and figures shells will be provided in a separate document.

9. REFERENCES

- NA

10. REVISION HISTORY

Version Number	Date	Description
1.0	25 July 2024	Initial release

11. APPENDIX 1. PROTOCOL SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessment	Screening	Cycle 1							Cycle 2							Cycle 3 +							EOT[a]	FUP[a]	sFUP[a]
Study Week		**1**			**2**		**3**		**1**			**2**		**3**		**1**			**2**		**3**				
Cycle Day	**-28 to -1**	1	2	5	8	11	15	18	1	2	5	8	11	15	18	1	2	5	8	11	15	18			
Time Window[b]	-	2	1	1	2	1	2	1	2	1	1	2	1	2	1	2	1	1	2	1	2	1	1	3	3
Informed consent	X																								
Eligibility	X																								
Medical history	X																								
Con. meds[c]	X	Throughout study																						X	
Pathology review[d]	X																								
Physical exam[e]	X	X							X							X							X		
Height	X																								
Weight[f]	X	X							X							X							X		
Vital signs	X	X							X							X							X		
ECOG PS	X	X							X							X							X		
Adverse events	X	Throughout study																						X	
Laboratory tests[g]	X	X			X		X		X			X		X		X			X		X		X		
HIV, hepatitis serologies	X																								
Urine/serum pregnancy test[h]	X	X[h]							X[h]							X[h]									
Urinalysis	X																						X		
ECG (single) for subjects not in the PK assessment[i]	X	X							X							X							X		
ECG (single) for subjects in the PK assessment[j]	X	X	X						X							X	X								
Tumor imaging[K]	X															X							X		
Survival		Throughout study																							X
PROs[l]	X	X							X							X							X		
Biomarker sampling[m]	X															X							X		
Blood for PK[n]		X	X						X							X	X								
Dispense unesbulin/placebo		X							X							X									
Study drug accountability[o]					X		X		X			X		X		X			X		X		X		
DTIC (IV)[p]		X							X							X									

Assessment	Screening	Cycle 1							Cycle 2							Cycle 3 +							EOT[a]	FUP[a]	sFUP[a]
Study Week		**1**			**2**		**3**		**1**			**2**		**3**		**1**			**2**		**3**				
Cycle Day	**-28 to -1**	1	2	5	8	11	15	18	1	2	5	8	11	15	18	1	2	5	8	11	15	18			
Time Window[b]	-	2	1	1	2	1	2	1	2	1	1	2	1	2	1	2	1	1	2	1	2	1	1	3	3
Unesbulin or placebo (PO) in clinic or home[q]			X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X			

Abbreviations: AE, adverse events; AIC, 5-amino-imidazole-4-carboxamide; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CMP, complete metabolic panel; Con., concomitant; DTIC, dacarbazine; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOI, end of infusion; EORTC QLQ-C30, 30-item score European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire; EOT, end-of-treatment; EQ-5D-5L, EuroQol 5-level EQ-5D version; FUP, follow-up; OS, overall survival; PK, pharmacokinetics; PROs, patient-reported outcomes; PS, performance status; RBC, red blood cell; SAE, serious adverse event; sFUP, survival follow-up; SOI, start of infusion; WBC, white blood count

[a] The EOT visit should be performed within 30 days after the end of treatment or until recovery from or stabilization of the AE, whichever occurs latest. The EOT imaging should be performed if the last scan was ≥3 weeks earlier. For subjects requiring immediate initiation of a new treatment option, the EOT visit may be completed earlier. A safety FUP assessment should be performed by phone at 30 days (±3 days) after the EOT to assess AEs and concomitant medications. sFUP assessments should be performed by phone every 3 months (±7 days) after the EOT until the later of 184 events or 2 years after the last subject has been randomized.

[b] Specified time window is ± days. Unesbulin/placebo should not be dosed on consecutive days, and preferably at least 3 days (72 hours) between each unesbulin/placebo dose. The window for completion of the activities associated with Cycle 1 Day 1 and Cycle 2 Day 1 may be divided between a 2-day span.

[c] Concomitant medications involve a complete medication reconciliation, including medications used for tolerability (eg, antiemetics and antidiarrheals).

[d] Pathology review to confirm the histologic diagnosis of leiomyosarcoma is required. An outside pathology report documenting leiomyosarcoma is acceptable.

[e] Full physical examination should be done at screening and EOT visits. Symptom-directed physical examination can be done at all other timepoints.

[f] Assess weight on the day of DTIC administration; modify dose of DTIC if >10% change from baseline (or the last time the dose was changed).

[g] Local laboratory testing is acceptable. Screening laboratory assessments and urinalysis must be collected within 3 weeks of Cycle 1 Day 1. Cycle 1 Day 1 laboratory assessments may be collected up to 24 hours before the first dose, but this window may be extended up to 72 hours for sites if it is impacted by laboratory working hours. For subsequent cycles, laboratory assessments may be collected up to 48 hours before dosing. On Day 1 Week 1 of each cycle, all laboratory assessments should be performed. On Day 1 of Weeks 2 and 3 of Cycles 1, 2, and 3, a CBC and CMP should be assessed for each subject. After Cycle 3, clinical laboratory assessments are required only once every cycle instead of on a weekly basis **unless there is an interruption in DTIC**. If DTIC is held due to toxicity (see Section 3.3), then laboratory assessments should be completed while dosing with unesbulin/placebo continues. If DTIC is interrupted or held, then laboratory assessments should be done within 24 hours of resuming dosing with DTIC **and continue on a weekly basis thereafter** to ensure that the subject meets the protocol-defined safety criteria in Section 3.3.

Laboratory tests include: (1) CBC (hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), WBC count, WBC differential (may be automated or manual as per institutional standards), RBC count, lymphocytes, monocytes, neutrophils, band neutrophils (if reported), eosinophils, basophils, platelets; and (2) CMP: albumin, alkaline phosphatase, total bilirubin, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, and sodium.

[h] **For women of childbearing potential, a serum pregnancy test should be performed at screening (with a window of 7 days) and a urine pregnancy test should be performed within 24 hours of Day 1 of Cycle 1. A urine or serum pregnancy test should be performed within 24 hours prior to dosing on Day 1 of Cycle 2 and continuing every 2 cycles beginning at Cycle 4.**

[i] **For subjects not participating in the PK assessment**, a single ECG should be collected on Day 1 of the first 3 treatment cycles only, approximately 2 hours after DTIC infusion. If DTIC is interrupted, then the single ECG should be collected approximately 2 hours after DTIC infusion and recorded on an unscheduled case report form page.

[j] **For subjects participating in the PK assessment**, a single ECG should be taken as follows:

- Predose and 1.5, 4, and 8 hours postdose on Day 1 of Cycles 1 and 3 concurrent with intensive PK sampling for DTIC/AIC.
- Predose and 2, 4, 6, and 8 hours postdose on Day 2 of Cycles 1 and 3 concurrent with intensive PK sampling for unesbulin.

- Approximately 2 hours after DTIC infusion on Cycle 2.

[k] Pretreatment, baseline imaging should be performed ≤14 days before Cycle 1 Day 1. On-treatment imaging should be performed every 6 weeks (±7 days). After Cycle 8, scans may be performed every 9 weeks. If any subject responds with a CR or PR at any assessment, then the subsequent confirmatory scan should be performed 4 weeks (+5 days) after the previous scan where the objective response was first evidenced. If the subject withdraws from the study for reasons other than progression of disease, EOT imaging should be performed if the last scan was ≥3 weeks earlier. Subjects should be followed with the same imaging procedure throughout the study. Computed tomography scans or magnetic resonance imaging may be used as clinically indicated.

[l] PROs include EORTC QLQ-C30 and EQ-5D-5L.

[m] Blood samples (10 mL) to assess circulating biomarkers will be collected at screening (predose) and prior to dosing on Day 1 of Cycle 3 and at the time of disease progression or EOT. Samples will be processed, stored, and shipped according to instructions in the laboratory manual.

[n] For subjects participating in the PK assessments:

- **PK for DTIC/AIC**: On Day 1 of Cycles 1 and 3, blood samples will be collected at predose, 0.5, 1.0 (within 10 minutes before EOI), 1.25 (approximately 15 minutes post EOI), 1.5, 2, 4, 8, 10, and 24 hours postdose (SOI). On Day 1 of Cycles 2 and 4, sparse blood samples will be collected at predose, 1.25, and 4 hours postdose (SOI). If DTIC is interrupted or held in Cycle 3, then the same intensive PK sampling schedule for DTIC should be followed on the day that DTIC resumes in the subsequent cycle. For PK assessments, DTIC must be administered the day before unesbulin/placebo dosing. DTIC should not be administered on the same day as unesbulin/placebo.
- **PK for unesbulin**: On Day 2 of Cycles 1 and 3, blood samples will be collected at predose, 1, 2, 3, 4, 6, 8, 10, and 24 hours postdose. PK sample collection, processing, storage, and shipment will be performed according to instructions outlined in the laboratory manual separate from this protocol. If DTIC is interrupted or held in Cycle 3, then the same intensive PK sampling schedule for unesbulin/placebo should be followed on the day after DTIC resumes in the subsequent cycle. For PK assessments, DTIC must be administered the day before unesbulin/placebo dosing. DTIC should not be administered on the same day as unesbulin/placebo.
- The collected PK samples may also be used for further exploratory analysis of unesbulin and DTIC metabolism.

[o] Subject medication diary is given to subjects to record unesbulin/placebo dosing at home and will be provided at Day 1 of each cycle or at other visits, as needed, to ensure compliance. Subject should bring the diary back at all scheduled visits for review with the research staff to assess treatment compliance.

[p] Within 30 minutes before DTIC administration, the following premedication regimen is recommended: fosaprepitant 150 mg IV once, dexamethasone 20 mg PO once, and ondansetron 16 mg PO once. The premedication regimen as per institutional practice is allowed. Please refer to Section 3.3 for instructions on DTIC interruptions and dose modifications due to toxicity.

[q] For subjects participating in the PK assessment, unesbulin/placebo will be administered at the clinic on the day of intensive PK sampling (Day 2 of Cycle 1 and Cycle 3 except in cases of DTIC interruption) and at home on other scheduled unesbulin/placebo dosing days. For all other subjects (ie, those not in the PK assessment), unesbulin/placebo should be taken by the subject at home.

Note: Treatment cycles will repeat until the subject meets the criteria for withdrawal from the study. All windows refer to business days (exclude weekends and holidays). Activities designed to be completed in a single day, such as PK sampling from before dosing to hour 8 postdose, may not be split up between the 2 days of a window.

If DTIC is interrupted and toxicity resolves as per criteria in Section 3.3, then clinical laboratory (ie, CBC and CMP) and body weight assessments must be performed within 24 hours prior to DTIC reintroduction. A single ECG must also be performed approximately 2 hours after reintroduction of DTIC if the interruption occurs within the first 3 treatment cycles. If DTIC is interrupted or held in Cycle 3, then the same intensive PK sampling schedule should be followed upon reintroduction of DTIC as described in footnote “n”.