CLINICAL TRIAL PROTOCOL

TITLE: **A Phase 1/2 Study to Investigate the Safety, Pharmacokinetics and Efficacy of Tinostamustine, a First-in-Class Alkylating Histone Deacetylase Inhibition (HDACi) Fusion Molecule, in Patients with Advanced Solid Tumors**

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PROTOCOL SIGNATURE PAGE

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By signing below, the Investigator agrees to adhere to the protocol as written and agrees that any changes to the protocol will be agreed to and approved by Mundipharma Research Limited. Prior to instituting those changes, the Investigator will obtain approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

This trial will be conducted in accordance with the current International Council for Harmonization (ICH) guidance, the Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, the United States (US) Food and Drug Administration (FDA) regulations and local IRB and legal requirements.

Investigator Signature _____ Date: _____

Name of Investigator (print) _____

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BSA	Body surface area
BUN	Blood urea nitrogen
CA	Competent Authority
CAP	College of American Pathologists
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CR	Complete response
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DME	Dose-modifying event
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunoassay
FA	Full analysis
FDA	Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
GCP	Good Clinical Practice

Abbreviation	Explanation
GGT	Gamma-glutamyl transaminase
GIST	Gastrointestinal stromal tumors
HDACi	Histone deacetylase inhibitor
HER2	Human epidermal growth factor receptor
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HPβCD	Hydroxyl-propyl-β-cyclodextrin
IV	Intravenous; Intravenously
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IME	Important medical event
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name
IRB	Institutional Review Board
ISH	In situ hybridization
LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
MAD	Maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro ribonucleic acid
MM	Multiple myeloma
MMMT	Malignant Mixed Mullerian Tumor
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	Objective response rate

Abbreviation	Explanation
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PFS	Progression free survival
Ph. Eur.	Pharmacopoeia Europaea
PI	Principal Investigator
PK	Pharmacokinetic
PMN	Polymorphonuclear
PO QD	orally, once daily
QT	A measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles.
QTc	Corrected QT interval
QTcF	QT corrected by Fredericia
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SADR	Serious Adverse Drug Reactions
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCLC	Small cell lung cancer
SD	Stable disease
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SRC	Safety Review Committee
STS	Soft tissue sarcoma
SUSAR	Suspected unexpected serious adverse reaction
TdP	Torsades de pointes
TEN	Toxic epidermal necrosis
TLS	Tumor lysis syndrome
T_{max}	Time to maximum concentration

Abbreviation	Explanation
TNBC	Triple negative breast cancer
ULN	Upper limit of normal
US, USA	United States, United States of America
USP	United States Pharmacopeia
WBC	White blood cell count

1 PROTOCOL SYNOPSIS

Title	**A Phase 1/2 Study to Investigate the Safety, Pharmacokinetics and Efficacy of Tinostamustine, a First-in-Class Alkylating Histone Deacetylase Inhibition (HDACi) Fusion Molecule, in Patients with Advanced Solid Tumors**
Protocol Number	EDO-S101-1002
Trial Sponsor	**Mundipharma Research Limited**
Objectives	**Phase 1:** Dose Escalation until Maximum Administered Dose (MAD): Primary objective: To determine the safety, tolerability, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of tinostamustine as a single agent in patients with solid tumors who have progressed after at least 1 line of therapy and for whom no other standard therapy with proven clinical benefit is available. The MTD was to be determined for intravenous (IV) administration on Day 1 and 15 of a 4-week treatment cycle. In October 2018, the Safety Review Committee recommended 80 mg/m^2 administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle as the dose for Phase 2. Secondary objective: • To establish the pharmacokinetic (PK) profile of tinostamustine. **Phase 2:** Evaluation of Response Rate in Selected Solid Tumor Cohorts: Primary objective: • To determine the objective response rate (ORR) [complete response (CR) plus partial response (PR)] of any duration, plus the rate of patients with stable disease (SD) of at least 4 months duration at a dose of 80 mg/m^2 administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle. Secondary objectives: • To evaluate safety and tolerability of 80 mg/m^2 of tinostamustine administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle.

	• To determine the progression free survival (PFS) time for patients who received 80 mg/m^2 of tinostamustine administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle. • To determine the overall survival time (OS) for patients who received 80 mg/m^2 of tinostamustine administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle. • To determine duration of response. • To establish the whole PK profiles of tinostamustine. Exploratory objective: • To correlate the extent of gene expression changes in tumor samples with anti-tumor activity.
Clinical Phase	Phase 1/2
Investigational Medicinal Product	Tinostamustine (EDO-S101)
No. of Patients	**Phase 1: Dose Escalation until MAD:** Total number of patients in the dose escalation scheme was expected to be 42 at the maximum (3 per cohort, at MTD 6 per cohort for 2 schedules and 6 dose levels). In October 2018, enrollment to Phase 1 closed with 22 patients treated with tinostamustine. **Phase 2: Evaluation of Toxicity and Response Rate in Selected Solid Tumor Cohorts**: Five (5) cohorts with 10 evaluable patients in each cohort expanding to a possible 29 in each cohort under a Simon 2-stage design[13], resulting in a sample size ranging from 56 to 160.
Number of Centers	Multicenter trial; 10-13 centers (Phase 1: 2 centers; Phase 2: 10-15 centers) in the United States, Canada and Europe will participate.
Trial Design	The trial is designed as an open label, Phase 1/2 trial of single agent tinostamustine. The Phase 1 portion of the trial was designed to define the MTD by evaluating toxicities during dose escalation until MAD. The Phase 2 portion of the trial is designed to evaluate ORR of the RP2D (80 mg/m^2 of tinostamustine administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle) at 4 or 6 months, depending on the type of solid tumor. Secondary objectives are evaluation of safety and tolerability of the RP2D in selected solid tumors. Patients will be eligible for this trial if they have a histologically confirmed solid tumor, sign informed consent and meet the inclusion/exclusion criteria. After

	enrollment, patients will be screened, and all procedures will be performed as per protocol. In Phase 1, tinostamustine doses were escalated following the standard 3+3 cohort design.[1] The decision to escalate to the next dose level occurred after all patients in a cohort had completed 1 cycle of therapy and were considered evaluable for safety and toxicity. A Safety Review Committee (SRC) that included the Investigators and Sponsor/sponsor's representatives reviewed available data including toxicity and activity data to reach consensus on dose levels and determination of the MTD and RP2D. The dose levels and schedules are defined in Section 3.2 and shown in Table 2. In the 3+3 design, if one of the 3 patients had a dose-limiting toxicity (DLT) (as defined below), the cohort was to be expanded to a maximum of 6 patients. If only one of the 6 patients had a DLT, dose escalation was to continue. If 2 patients have a DLT, dose escalation was to stop, regardless of the number of patients that had been treated in this cohort. If 2 or more DLTs occurred in a 6-patient cohort, this dose was declared the MAD. A decision was to be taken by the Sponsor and SRC to open intermediary dose levels below the MAD to better define the MTD. The MTD was confirmed when 6 patients were treated at a dose level with less than 2 DLTs. In case a patient experienced a DLT at dose level one (60 mg/m^2) at any administration schedule, the Investigational Medicinal Product was to be reduced one dose level to 40 mg/m^2. In October 2018, the SRC recommended 80 mg/m^2 administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle as the RP2D. During Phase 1, the PK characteristics of tinostamustine, and its 2 metabolites M2 and M8, were to be determined at all dose levels. Blood samples for PK determinations were obtained in Cycle 1 at each time of Investigational Medicinal Product (IMP) administration, from each patient. The second phase of the trial (Phase 2) is designed to evaluate ORR of the RP2D (80 mg/m^2 of tinostamustine administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle) at 4 or 6 months in cohorts of patients with defined solid tumors. Five cohorts will be opened to recruit patients with: (1) relapsed/refractory small cell lung cancer (SCLC) (2) relapsed/refractory soft tissue sarcoma (STS) (3) relapsed/refractory triple-negative breast cancer (TNBC)* (4) relapsed/refractory ovarian cancer (5) relapsed/refractory endometrial cancer* **On 05 March 2021, following an evaluation of the development of EDO-S101 (Tinostamustine) across multiple studies, the Sponsor has taken the decision to halt recruitment into the Cohorts for relapsed/refractory triple-negative breast cancer (TNBC)*

	and relapsed/refractory endometrial cancer on this study. This decision was made to enable focusing of resources into a defined and select set of patient cohorts. Each cohort will recruit 10 patients who will be treated at 80 mg/m^2 administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle and monitored for safety and efficacy. Each cohort may treat an additional 19 patients (29 in total) if there is evidence of 2 successes in that cohort. Success is defined as either a CR or a PR of any duration, or SD of at least 4 months duration. The Sponsor may suspend or discontinue enrollment to an expansion cohort at any time due to slow patient accrual rates or other reasonable cause. In Phase 2, the PK profile of tinostamustine and its 2 metabolites, M2 and M8, will be assessed in Cycle 1 in a minimum of 50 patients. Treatment may continue until progression or intolerable toxicity, up to a maximum of 12 cycles. Investigator and the Sponsor may decide to reduce a patient's dose to 60 mg/m^2 in case of safety concerns. If toxicity issues are resolved, the original dose can be administered at the next cycle. If the patient cannot tolerate the reduced dose, then the patient will be withdrawn from the study. Patient assessments, except for imaging studies, will be performed at the end of each treatment cycle and at the time of Investigational Medicinal Product discontinuation (at any time or Day 28 of the last treatment cycle). Tumor response assessment by imaging will be performed at baseline and every 2 cycles during treatment and every 2 months after stopping treatment according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (Section 13.3).
Stopping Rules	**Stopping Rules (Phase 1):** To ensure patients' safety, stopping rules were applied in Phase 1. If 66% or more patients treated at any given time of the dose escalation part of the trial experienced the following Grade 2 toxicities, the trial was to be stopped for enrollment and the risk assessed and addressed by the Sponsor. • Grade 2 venous thrombosis • Grade 2 increase of serum creatinine (>1.5 - 3.0 x upper limit of normal [ULN]) • Grade 2 nervous system disorders excluding headache **Stopping Rules for Phase 2** Stopping rules in Phase 2 apply for patients who experience QTc prolongations >500 ms or change from baseline >60 ms (Grade 3) that are not

	transient or occur in more than 1 treatment cycle. If the QTcF value on the electrocardiogram (ECG) machine printout is >500 ms or represents an increase > 60 ms from baseline, 2 additional ECGs are to be performed approximately 1 minute apart. If the average QTcF of the 3 ECGs is >500 ms or increased > 60 ms from baseline, the tinostamustine infusion must be stopped. The patient should stay in the unit until the QTcF has decreased to baseline. In addition, the patient is to be continuously observed for syncope or other clinically relevant cardiac events. A thorough evaluation of ECGs, including expedited central review of Grade 3 QTc prolongations by an independent assessor, will be performed. The decision will then be made by the Investigator in consultation with the Medical Monitor, whether tinostamustine treatment is to continue, be postponed or be stopped. (Refer to Section 8.7, Dose modification guidelines and stopping rules, for the management of patients who experience clinically significant QTcF prolongations).
• **Trial Population Phase 1 and 2**	**General Inclusion Criteria for Phase 1 and Phase 2 portions of Trial:** • Patient willing and able to sign the informed consent. • Patients age ≥18 years at signing of the informed consent. • Life expectancy > 3 months. • Histologically confirmed diagnosis of advanced or metastatic solid tumors, disease should have progressed during or following at least 1 previous line of therapy and no other standard therapy with proven clinical benefit is available or recommended based on the investigator's individual risk-benefit assessment for the patient. • Patients with secondary metastasis to the central nervous system (CNS) are eligible if they have had brain metastases resected or have received radiation therapy ending at least 4 weeks prior to trial day 1 and they meet all of the following criteria: (1) Residual neurological symptoms ≤ Grade 1 (2) No glucocorticoids requirement or patients may be receiving low doses of glucocorticoids providing the dose has been stable for at least 2 weeks prior to starting the trial medication (Section 7.14.1) (3) Follow-up imaging studies show no progression of treated lesions and no new lesions • Evaluable disease; measurable on imaging as assessed by RECIST version 1.1.

	• Eastern Cooperative Oncology Group (ECOG) performance status ≤2 (Section 13.1). • Absolute neutrophil count (ANC) (polymorphonuclear [PMN] cells plus bands) >1,000 / µL. • Platelets ≥100,000 / µL. Platelet transfusions within the 14 days before Day 1 of Cycle 1 is prohibited. • Aspartate aminotransferase/alanine aminotransferase (AST/ALT) ≤3× upper limit of normal (ULN). In cases with liver involvement ALT/ AST ≤5× ULN. • Total bilirubin ≤1.5 mg/dL unless elevated due to known Gilbert's syndrome. • Creatinine ≤1.5 ULN. • Serum potassium and magnesium at least at the lowest limit of normal (LLN) range, before every IMP administration. If it is below LLN, supplementation is permissible. • Female study participants of child-bearing potential and their partners, and male study participants who intend to be sexually active with a woman of child-bearing potential, must be willing to use at least TWO highly effective forms of contraception. This should start from the time of study enrollment and continue throughout IMP administration. Female study participants of child-bearing potential must continue using contraception for at least six months after the last administration of the IMP. Female study participants should be willing to have a pregnancy test performed at screening, ≤ 1 day prior to day 1 of each IMP administration and at study treatment discontinuation. Male study participants who are sexually active with a woman of child-bearing potential should also use a condom during treatment and for at least ninety (90) days after the last administration of IMP. Vasectomized males are considered fertile; therefore, vasectomized partners and patients must be willing to use a secondary method of effective birth control. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. **Exclusion Criteria for Phase 1 and Phase 2 portions of Trial:** • Patients with primary central nervous system (CNS) cancer. • Patients with QTc interval (Fridericia's formula) >450 ms.

	• Patients who are on treatment with drugs known to prolong the QT/QTc interval. Refer to CredibleMeds list of drugs with known risk of Torsade des pointes (TdP): http://crediblemeds.org/new-drug-list. • Patients who are being treated with Valproic Acid for any indication (epilepsy, mood disorder). • Any serious medical condition that interferes with adherence to trial procedures. • Prior history of another solid tumor malignancy diagnosed within the last 3 years of trial enrollment excluding adequately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or *in situ* cervical cancer, *in situ* breast cancer, *in situ* prostate cancer (patients must have shown no evidence of active disease for 2 years prior to enrollment) • Pregnant or breastfeeding women. • New York Heart Association (NYHA) stage III/IV congestive heart failure (Section 13.2). The following arrhythmias: atrial fibrillation/flutter with poor rate control, documented sustained ventricular tachycardia (defined as >30 seconds or requiring cardioversion before 30 seconds have elapsed) or TdP. • Significant co-morbidities (e.g., active infection requiring systemic therapy, history of human immunodeficiency virus [HIV] infection, or active Hepatitis B or Hepatitis C). • Use of other investigational agents or previous anticancer therapies within 28 days prior to the first dose of tinostamustine, provided the patient has recovered from any related toxicities ≥Grade 1. • Steroid treatment within 7 days prior to trial treatment. Patients that require intermittent use of bronchodilators, topical steroids, or local steroid injections will not be excluded from the trial. Patients who have been stabilized to 10 mg prednisolone orally (PO) once daily (QD) (or equivalent), daily (or less) at least 7 days prior to Investigational Medicinal Product administration are allowed.
Trial Population (Phase 2)	**Specific Eligibility Criteria for Each Patient Cohort in <u>Phase 2</u> portion of the Trial** Phase 2 patients must meet the cohort-specific inclusion/exclusion criteria in addition to the general inclusion/exclusion criteria previously noted. Confirmation of the availability of a tumor sample from the primary or recurrent cancer must be provided (archival samples are acceptable).

	Cohort 1: Relapsed/Refractory Small Cell Lung Cancer 1. Histologically or cytologically confirmed limited or extensive disease stage of SCLC. 2. Must have received at least 1 line of prior combination chemotherapy or biological therapy and no other standard therapy with proven clinical benefit is available or recommended based on the investigator's individual risk-benefit assessment for the patient. 3. At least 28 days should have elapsed since prior treatment as long as the patient has recovered from any related toxicities to ≤ Grade 1 (or ≤ Grade 2 for any symptomatic neuropathy or endocrinopathies). 4. Prior radiotherapy is acceptable provided the patient has recovered from any radiotherapy related acute toxicities. 5. The disease should be progressing during or relapsing after the previous treatment. 6. Presence of measurable disease as defined by RECIST version 1.1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. **Cohort 2: Relapsed/Refractory Soft Tissue Sarcoma** 1. Histologically confirmed diagnosis of advanced, unresectable, or metastatic STS not amenable to curative treatment with surgery or radiotherapy excluding: neuroblastoma, GIST, embryonal rhabdomyosarcoma, Kaposi sarcoma, chondrosarcoma, osteosarcoma or Ewing's sarcoma. 2. Must have received at least 1 prior line chemotherapy or biological therapy regimen and no other standard therapy with proven clinical benefit is available or recommended based on the investigator's individual risk-benefit assessment for the patient. At least 28 days should have elapsed since prior chemotherapy as long as the patient recovered from any related toxicities to ≤ Grade 1 (or ≤Grade 2 for any symptomatic neuropathy or endocrinopathies). 3. The disease should be progressing during or relapsing after the previous treatment. 4. Presence of measurable disease as defined by RECIST version 1.1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered

	measurable unless there has been demonstrated progression in the lesion. **Cohort 3: Relapsed/Refractory Triple Negative Breast Cancer** ***RECRUITMENT INTO THIS COHORT HAS NOW BEEN HALTED*** **Cohort 4: Relapsed/Refractory Ovarian Cancer** 1. Histologically or cytologically confirmed advanced ovarian cancer epithelial ovarian cancer including primary peritoneal cancer or fallopian tube cancer (excluding borderline ovarian cancer, malignant mixed Mullerian tumor (MMMT)) of high grade serous histology, or high grade endometrioid cancer, that is resistant or refractory to platinum therapy and no other standard therapy with proven clinical benefit is available or recommended based on the investigator's individual risk-benefit assessment for the patient. Clear cell carcinomas are excluded. Patients with primary platinum refractory disease (failure to respond to initial platinum treatment or relapse within 4 weeks) and patients with primary platinum resistant disease (progression within 6 months of completing first line platinum-based therapy) are excluded from the study. 2. At least 28 days should have elapsed since prior chemotherapy, as long as the patient recovered from acute toxicity of previous therapies to ≤ Grade 1 (or ≤ Grade 2 for any symptomatic neuropathy or endocrinopathies). 3. The disease should be progressing during or relapsing after the previous treatment. 4. Presence of measurable disease as defined by RECIST version 1.1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. **Cohort 5: Relapsed/Refractory Endometrial Cancer** ***RECRUITMENT INTO THIS COHORT HAS NOW BEEN HALTED***
Dose and Schedule	The starting dose in Phase 1 was 60 mg/m^2 and the escalation schedule was selected based on the experience from the ongoing First-in-human Phase 1 trial in patients with relapsed/refractory hematologic malignances. The dose selected for Phase 2, based on Phase 1 data, is 80 mg/m.^{2} administered over a 60-minute infusion, on D1 and D15 of a 4-week cycle.

Phase 1

Dose Escalation Plan

Dose escalation for each patient was conducted according to the following schemes:

Dose Level	Tino-stamustine Dose	Administration	Schedule
-1*	40 mg/m^2	30 min infusion	D1 and D15 every 28 days
1 – Starting Dose	60 mg/m^2	30 min infusion	D1 and D15 every 28 days
2	80 mg/m^2	30 min infusion	D1 and D15 every 28 days
3	100 mg/m^2	30 min infusion	D1 and D15 every 28 days
4**	60 mg/m^2	60 min infusion	D1 and D15 every 28 days
5	80 mg/m^2	60 min infusion	D1 and D15 every 28 days
6***	100 mg/m^2	60 min infusion	D1 and D15 every 28 days

*If a patient experienced a DLT at dose level one (60 mg/m^2), tinostamustine was to be reduced one dose level to 40 mg/m^2.

** If a patient experienced a DLT at the 60 mg/m^2, 60-minute infusion dose-level, tinostamustine was to be reduced one dose level to 40 mg/m^2, 60 minutes infusion time.

***Additional dose escalations were to be considered until the MAD was reached.

Phase 2

Evaluation of Toxicity and Response Rate in Selected Solid Tumor Cohorts

The Phase 2 portion of the trial will follow a Simon 2-stage design. The RP2D (80 mg/m^2 administered over 1 hour (± 5 minutes) on Day 1 and 15 of each 4-week treatment cycle) will be further investigated in patients with specific types of solid tumors. There will be 5 cohorts, each with 10 patients and potentially increased up to 29 patients, and each with the following tumor type:

- Cohort 1: Relapsed/refractory SCLC
- Cohort 2: Relapsed/refractory STS
- Cohort 3: Relapsed/refractory TNBC*
- Cohort 4: Relapsed/refractory ovarian cancer

	• Cohort 5: Relapsed/refractory endometrial cancer* **On 05 March 2021, following an evaluation of the development of EDO-S101 (Tinostamustine) across multiple studies, the Sponsor has taken the decision to halt recruitment into the Cohorts for relapsed/refractory triple-negative breast cancer (TNBC) and relapsed/refractory endometrial cancer on this study. This decision was made to enable focusing of resources into a defined and select set of patient cohorts.* In stage 1, 10 patients will be treated in each cohort, potential efficacy and the decision to expand into stage 2 or not may be taken prior to the 10th patient completing the study. During the assessment of stage 1, enrollment into the expanded cohort (stage 2) will continue. If there are no successes or only 1 success in the first 10 patients enrolled into each specific stage 1 cohort, recruitment to that cohort will be stopped. If there are 2 or more successes in the first 10 patients enrolled in a given cohort, up to an additional 19 patients may be treated in stage 2 to a total of 29. If it becomes clear that there will be 5 or fewer successes in a cohort of 29 patients, then the cohort will be stopped for lack of efficacy. In each cohort, a success is defined as: CR or PR of any duration, or SD that persists for at least 4 months The Sponsor may suspend or discontinue enrollment to an expansion cohort at any time due to slow patient accrual rates or other reasonable cause.
Duration of Trial/ Patient Participation	In October 2018 enrollment to Phase 1 closed with 22 patients treated with tinostamustine. The total number of patients who will participate in the Phase 2 portion of the trial is expected to be between 56 and 160. The total number of participants is expected in both Phases 1 and 2 to be 182 at maximum. The duration of Phase 2 of the trial is expected to be approximately 24 months for patient enrollment and treatment with 12 months of follow up for a total duration of 36 months.
Safety Evaluations	Safety assessments include physical examinations, ECOG performance status determinations, electrocardiograms (ECGs), pregnancy testing for women of child-bearing potential, documentation of adverse events (AEs), clinical laboratory evaluations including hematology, blood chemistry and urinalysis, vital signs, and documentation of concomitant medication usage. Toxicities in both stages of the trial are assessed for severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, June 2010, with the exception that in Phase 2, assessment of QTc prolongations constituting AEs of special interest are

	based on CTCAE version 5.0.
Efficacy Evaluations	Efficacy evaluations in Phase 2 will include ORR (i.e., patients with a CR plus patients with a PR of any duration), rate of patients with SD of at least 4 months duration, duration of response, PFS, and OS. Radiologic response assessment by computed tomography (CT) or magnetic resonance imaging (MRI) will be performed at baseline and every 2 cycles during treatment and every 2 months after stop of treatment. Tumor response will be evaluated according to RECIST version 1.1 (Section 13.3).
Pharmacokinetic Assessments	Plasma samples will be collected to determine the concentrations of tinostamustine, and its 2 metabolites M2 and M8, by a method fully validated according to the relevant guidelines. In Phase 1, the PK profiles of tinostamustine in plasma were assessed in each patient during the escalation phase, and in Phase 2, a minimum of 50 patients will be assessed. Blood sampling will occur in Cycle 1 only at each drug administration. The schedule is provided in Section 7.16 of this protocol.
Pharmacodynamic Evaluations	Patient participation in the gene expression analysis is not mandatory for enrollment into the trial. If the patient agrees to participate in the gene expression analysis, a fresh or archival tissue sample will be collected during screening. Formalin fixed paraffin embedded (FFPE) biopsy samples will be used. The Affymetrix chip technology for analyzing total ribonucleic acid (RNA) will be used. For formalin fixed paraffin embedded samples, RecoverAll method from Ambion® for isolating total RNA will be used. The isolated RNA is total RNA and will contain both messenger RNA (mRNA) and micro RNA (miRNA). The expression profile will be analyzed for correlation with response or resistance to therapy. Details of sample preparation and shipping are described in the Laboratory Manual.
Sample Size Determination, Analyses	For Phase 1 a formal sample size determination and power calculation were not performed. Based on experience from previously published similar trials, a total number of 42 patients at maximum in the dose escalation stage of the trial was considered to be sufficient for meeting the objectives of this trial. In Phase 2, 56 to 160 patients (10 or 29 evaluable patients in each of the disease cohorts) are considered to be sufficient for meeting the objectives of this trial, following Simon's optimal 2-stage design methodology.[13] Assuming the proportion of treatment successes that do not warrant further investigation (π_0) is 0.10, the proportion of treatment successes that warrant further investigation (π_1) is 0.30, an 80% power and a 5% Type I error rate.

	In stage 1, 10 patients will be treated in each cohort; potential efficacy and the decision to expand into stage 2 or not may be taken prior to the 10th patient completing the study. During the assessment of stage 1, enrollment into the expanded cohort (stage 2) will continue. However, it is anticipated that new patients will enroll infrequently due to the expected low recruitment rate. From stage 1, if there are no successes or only 1 success in the 10 stage 1 patients, the complete cohort will be stopped for lack of efficacy. If there are 2 or more successes in stage 1 an additional 19 patients may be treated for a total of 29 in a cohort. If it becomes clear that there will be 5 or fewer successes in a cohort of 29 patients, then the cohort will be stopped for lack of efficacy.

2 SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

Procedure	Screening 28 days from Baseline (First Day Investigational Medicinal Product Administration); Scans 28 days from Baseline[15]	Cycle 1 and Subsequent Cycles[1]					Investigational Medicinal Product Discontinuation (at any time or Day 28 of last cycle)[14]	Follow-up[12,13]
		Day 1[14]	Day 2[14]	Day 15[14]	Day 16[14]	Day 22[14]		
Informed Consent	X							
Eligibility Criteria	X							
Demographics and Medical History (including prior cancer therapies)	X							
Complete Physical Examination	X	X					X	
Abbreviated Physical Examination[15]				X		X		
Weight and Height[2]	X	X						
Vital Signs[3]	X	X		X		X	X	
ECOG Performance Status	X	X		X		X	X	
12-lead ECG Assessments (Safety and Holter)[4]	X	X		X			X	
PK Assessments[5]		X[5]	X[1]	X[5]	X[1]			
Gene Expression Profiling[6]	X							

Procedure	Screening 28 days from Baseline (First Day Investigational Medicinal Product Administration); Scans 28 days from Baseline[15]	Cycle 1 and Subsequent Cycles[1]					Investigational Medicinal Product Discontinuation (at any time or Day 28 of last cycle)[14]	Follow-up[,12,13]
		Day 1[14]	Day 2[14]	Day 15[14]	Day 16[14]	Day 22[14]		
Hematology[7]	X	X		X		X	X	
Serum Chemistry[8]	X	X		X			X	
Urinalysis	X						X	
Pregnancy Test (urine or serum)[9]	X	X					X	
Baseline and Response Assessments[10, 12]	X						X	
Record AEs		X	X	X	X	X	X	
Assessment of Infusion Site and potential allergic reactions[11]		X		X				
Record Concomitant Therapies and Procedures	X	X		X		X	X	
Investigational Medicinal Product Administration		X		X				
Obtain PFS Information[12]								X
Survival Follow-up								X[13]

[1] Visits on Day 2 and 16 in Cycle 1 only: 24h (±2 h) from the start of infusion the day before.

[2] Height will be measured at screening or baseline only. The weight will be measured at screening and on Day 1 of each cycle. The documentation of weight will be used for Investigational Medicinal Product calculations of BSA. BSA will be calculated using the DuBois formula for each patient at the site.

[3] Resting supine blood pressure, pulse, respiratory rate, and temperature will be measured at Screening, Day 1, 15, and 22, and at trial discontinuation. On each treatment day blood pressure, pulse, and respiratory rate will be recorded pre-dose, 3 (±10 minutes), and 6 (±10 minutes) hours from the start of the tinostamustine infusion. Temperature will be recorded at pre-dose on each treatment day. After Cycle 1 the vitals for the 3- and 6-hour time points are considered optional assessments and should be done at the Investigator's discretion. If the 3- and 6-hour time points are not done, the Investigator must provide adequate instruction to the patient regarding potential allergic reactions, and this should be clearly documented in the patient chart.

[4] All ECGs will be obtained digitally using a Global Instrumentation (Manlius, NY, USA) M12R ECG and are to be performed after the patient is supine for 10 minutes A triplicate ECG will be performed during Screening (at least 1-2 minutes between each measurement) will be read centrally to determine patient eligibility for the trial. A triplicate ECG is to be performed before tinostamustine administration on D1 (i.e., day of tinostamustine dosing) in each cycle. Furthermore, patients are to have single ECGs performed at 30 minutes and triplicate at 60 minutes from the start of tinostamustine administration on D1 and D15 each treatment cycle and a single ECG on D28 (±2 days) of last treatment cycle. Additional ECGs may be conducted as clinically indicated.

Holter monitoring will commence 60 minutes prior to the start of tinostamustine infusion on C1D1 and 15 min prior to the start of tinostamustine infusion on C1D15 and will continue through 24 hours from the start of infusion. Replicate 10 second, 12-lead ECGs will be extracted from the continuous recording at each of the following time points on C1D1 and C1D15:

- C1D1: -45, -30, -15 minutes predose, and 15, 30, 45, 60, 75, 90, 120, 180, 360 minutes and 24 hours from the start of tinostamustine infusion.
- C1D15: prior to the start of infusion, and 15, 30, 45, 60, 75, 90, 120, 180, 360 minutes and 24 hours from the start of tinostamustine infusion.

[5] The blood sampling schedule for the PK assessment is conducted on Day 1 and 15 of Cycle 1 only. Samples are taken as follows: up to 0.5 hours prior to dose administration and at 15, 30 and 45 minutes, 1 hour, 75 and 90 minutes, and 2, 3, 6, and 24 hours from the start of the tinostamustine infusion. Samples will be taken at the same time and as close to the exact time point as possible, with sample draw windows: 15, 30, 45 (±5 minutes) 60 (-5 minutes as close to the calculated end of the IMP infusion as possible and before the end of IMP infusion), 75, and 90 minutes (±5 minutes); 2, 3 and 6 hr (±10 minutes), and 24 hr (±2 hr). In Phase 1, the PK profiles of tinostamustine in plasma were assessed in each patient during the escalation phase and in Phase 2, a minimum of 50 patients will participate in the PK analysis.

[6] Patients will be requested to participate to gene expression research. Information on the purpose of genetic research in the gene-expression sub-trial is provided, either in the main ICF or a separate ICF, based on applicable regulatory requirements, to allow the patient to decide whether he or she want to participate in this part of the trial. Participation in this genetic research is voluntary. See Section 7.9 and the Laboratory Manual for tumor sample requirements.

[7] Hematology will include white blood cell count (WBC) and differential, RBC, hemoglobin, hematocrit, platelets and absolute neutrophil count (ANC). Blood samples will be collected at Screening, Days 1 (- 2 days), 15 (- 2 days) and 22 (+/- 2 days) of each cycle, from cycle 1 to the last cycle of treatment, prior to IMP administration on Days 1 & 15, and at the time of IMP discontinuation (at any time or Day 28 of the last treatment cycle). Results should be reviewed prior to IMP administration.

[8] Serum chemistry will include albumin, total protein, creatinine, uric acid, blood urea nitrogen (BUN), sodium, potassium, magnesium, calcium, glucose, total bilirubin, alkaline phosphatase, AST, ALT, gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH) and C-reactive protein (CRP). Blood samples will be collected at Screening, Days 1 (- 2 days), 15 (- 2 days) and 22 (+/- 2 days) of each cycle, from cycle 1 to the last cycle of treatment, prior to IMP administration on Days 1 & 15, and at the time of IMP discontinuation (at any time or Day 28 of the last treatment cycle). Results should be reviewed prior to IMP administration. If potassium and/or magnesium levels before tinostamustine infusion are lower than normal they would need to be corrected and rechecked before the infusion proceeds.

[9] Women of childbearing potential is defined as a female who does not meet the criteria for "Women Not of Childbearing Potential": women ≥55 years of age and 12 consecutive months without menstrual bleeding, or ≤55 years of age after surgical sterilization.

[10] Patients will have a baseline tumor assessment done within the 28 days (with a 7-day window) prior to Cycle 1, Day 1. Response assessment by imaging after Cycle 2, 4, and 6, (8, 10 and 12 if applicable). In addition, the response assessment may be performed at any time according to symptoms and clinical judgment of the treating physician.

[11] Assessment of infusion site reactions must be performed on each treatment day at pre-dose, 1 hr (±15 min). The patient will be observed at 1 hr (±15 min post dose) for potential allergic reactions (See Section 8.10 for possible infusion reactions). The Investigator must provide adequate instruction to the patient regarding potential allergic reactions, and this should be clearly documented in the patient chart.

[12] For patients who discontinue trial treatment for reasons other than PD, tumor assessments per RECIST will be performed every 8 weeks (± 2 weeks) until documentation of disease progression or the initiation of a subsequent anti-cancer therapy, whichever comes first.

[13] Patients will be contacted every 3 to 4 months for the subsequent use of anti-cancer therapy as well as survival until 1 year after the last patient's first treatment (C1D1).

[14] Scans should be done within 28 days of baseline (with a 7-day window). The window for visits on Day 15 and 22 in cycle 1 is +/-1 day; the window for visits in cycle 2 onwards is +/-2 days, unless the tinostamustine dose is delayed due to toxicity (see Section 8.6).

[15] Abbreviated physical examination is directed by disease site and symptoms.

3 INTRODUCTION

3.1 Background

Initially regarded as “epigenetic modifiers” acting predominantly through chromatin remodeling by maintaining histone acetylation, histone deacetylase (HDAC) inhibitors (HDACi) are recognized to exert multiple cytotoxic actions in cancer cells, often through acetylation of non-histone proteins. Some well-recognized mechanisms of HDACi lethality include, in addition to relaxation of DNA and de-repression of gene transcription, interference with chaperone protein function, free radical generation, induction of deoxyribonucleic acid (DNA) damage, up-regulation of endogenous inhibitors of cell cycle progression, e.g., p21, and promotion of apoptosis. This class of agents is relatively selective for transformed cells, at least in nonclinical trials. In recent years, additional mechanisms of action of these agents have been uncovered. For example, HDACi compounds interfere with multiple DNA repair processes, as well as disrupt cell cycle checkpoints, critical to the maintenance of genomic integrity in the face of diverse genotoxic insults. Despite their nonclinical potential, the clinical use of HDAC inhibitors remains restricted to certain subsets of T-cell lymphoma. Currently, it appears likely that the ultimate role of these agents will lie in rational combinations, only a few of which have been pursued in the clinic to date.[3]

Multiple lines of recent data have begun to suggest that there is biologically important synergy that exists between alkylating agents and HDAC inhibitors. For example, in one trial the combination of bendamustine, an alkylating agent, and entinostat, a HDAC inhibitor, synergistically inhibits proliferation of multiple myeloma (MM) cells via induction of apoptosis and DNA damage response. In this trial, cell growth assays showed that bendamustine or entinostat inhibited proliferation in a dose-dependent manner, and their combinations synergistically induced growth inhibition in all MM cells tested. An apoptotic enzyme-linked immunoassay (ELISA) and western blot assays on poly (ADP-ribose) polymerase (PARP) cleavage and caspase-8 and caspase-3 revealed that bendamustine in combination with entinostat exhibited a much more potent activity than either agent alone to promote the MM cells undergoing apoptosis in a dose-dependent manner. Flow cytometric analysis found that entinostat exhibited distinct effects on cell cycle progression in different lines and bendamustine mainly arrested the cells at S phase, whereas their combinations dramatically blocked the S cells entering G2/M phase. Furthermore, trials on DNA damage response indicated that phosphohistone H2A.X (P-H2A.X), a hallmark of DNA double strand break, along with phosphorylated CHK2 (P-CHK2) was significantly enhanced by the combinations of bendamustine and entinostat as compared to either agent alone. These molecular changes were correlated with the increases in mitotic catastrophe.[4]

Tinostamustine is a first in class alkylating HDAC inhibitor that is being developed for the treatment of relapsed/refractory hematologic malignancies and solid tumors. The compound underwent broad evaluation in nonclinical models for human cancer. In *in vitro* and *in vivo* trials demonstrate efficacy in models of Hodgkin lymphoma, aggressive non-Hodgkin lymphoma, multiple myeloma, T-cell lymphoma and acute myeloid leukemia. In solid tumors activity was seen in models of sarcoma, small cell lung cancer (SCLC), non-small cell lung cancer, breast cancer, ovarian cancer and glioblastoma. The efficacy was independent from p53 status and cell lines resistant to other chemotherapy agents still responded to tinostamustine, including cell lines particularly resistant to bendamustine. Mechanistically, tinostamustine induces a strong DNA damage response, evidenced by a rise of ɣ-

pH2AX and p53, while DNA damage response was suppressed. Consequently, in vitro experiments showed synergy with DNA repair influencing agents such as PARP inhibitors.

3.2 Rationale for Dose and Schedule

A weekly administration achieving exposure at or over 1 μM of tinostamustine was more effective in solid tumor models than dosing once every 3 weeks. The starting dose in Phase 1 of 60 mg/m^2 was set following the experience that doses of 20, 40, 60, and 80mg/m^2 and 100mg/m^2 given once every 3 weeks have been administered safely to humans in an ongoing First-in-human Phase 1 trial in relapsed/refractory hematological malignancies. Tinostamustine will be given intravenously (i.v.) on Day 1 and 15 in a 4-week cycle.

The overall risk associated with tinostamustine treatment is expected to be similar to other alkylators, like bendamustine. The profile of toxicity seen in the nonclinical studies was similar to the toxicity seen in patients treated with bendamustine. In a series of phase I trials performed with bendamustine in patients with solid tumors various doses and schedules were evaluated as shown in the table below. DLTs occurred at various doses between 90 mg/m^2 and 280 mg/m^2 depending on the frequency of dosing.

Author	**Bendamustine Schedule**	**MTD**	**RP2D**	**DLT**	**Organ Toxicity**
Schoffski[4]	weekly for 8 consecutive weeks	80 mg/m^2	60 mg/m^2	fatigue, mouth dryness	NA
Schoffski[5]	D1 and D8 every 4 weeks	160 mg/m^2	140 mg/m^2	fatigue, mouth dryness	mild cardiac arrhythmia
Rasschert[6]	D1 every 3 weeks	280 mg/m^2	260 mg/m^2	fatigue, cardiac toxicity	cardiac
Rasschert[7]	D1 and D2 every 3 weeks	180 mg/m^2	160 mg/m^2	febrile neutropenia, thrombocytopenia	NA

3.3 Trial Rationale

The ability to fuse discrete small molecules with different types of pharmacologic activity has created remarkable opportunities in drug discovery and development. Bendamustine itself is a fusion molecule of the nitrogen mustard mechlorethamine and a purine analog based on fludarabine that exhibits unique activity where cancer cells have become resistant to conventional alkylating agents. In fact, randomized clinical trials have established that the combination of rituximab and bendamustine exhibits less toxicity and greater efficacy compared to a conventional R-CHOP based regimen. This concept opens the prospect that other rational fusion molecules could exhibit activity even greater than that seen in the parent molecule.

Tinostamustine is a unique new chemical entity. In the current and ongoing first-in-human dose escalation trial, some patients with relapsed or refractory hematological malignancies, for which there

are no available approved therapies, benefited from treatment. The benefit risk assessment is in favour of further development of this molecule in humans.

This clinical trial represents the first in human experience in patients with solid tumors with this novel first in class drug.

4 TRIAL OBJECTIVES

4.1 Primary Objectives

Phase 1: Dose Escalation until Maximum Administered Dose (MAD) (Complete):

- To determine the safety, tolerability, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of tinostamustine as a single agent in patients with solid tumors who have progressed after at least 1 line of therapy and for whom no other standard therapy with proven clinical benefit is available. The MTD was to be determined for i.v. administration on Day 1 and 15 of a 4-week treatment cycle.

  In October 2018, the Safety Review Committee recommended 80 mg/m^2 administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle as the dose for Phase 2.

Phase 2: Evaluation of Response Rate in Selected Solid Tumor Cohorts

- To determine the objective response rate (ORR) [complete response (CR) plus partial response (PR)] of any duration, plus the rate of patients with stable disease (SD) of at least 4 months duration at a dose of 80 mg/m^2 administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle.

4.2 Secondary Objectives

Phase 1: Dose Escalation until MAD (Complete):

- To establish the pharmacokinetic (PK) profile of tinostamustine.

Phase 2: To evaluate safety and tolerability of 80 mg/m^2 of tinostamustine administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle.

- To determine the progression-free survival (PFS) time for patients who received 80 mg/m^2 of tinostamustine administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle.
- To determine the overall survival (OS) for patients who received 80 mg/m^2 of tinostamustine administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle.
- To determine duration of response.
- To establish the whole PK profiles of tinostamustine.

4.3 Exploratory Objective

- To correlate the extent of gene expression changes in tumor samples with anti-tumor activity.

5 TRIAL DESIGN

5.1 Overall Trial Design

The trial is designed as an open label, Phase 1/2 trial of single agent tinostamustine. The Phase 1 portion of the trial aimed to define the MTD, the PK of tinostamustine and its 2 metabolites, M2 and M8 and to identify the RP2D. The Phase 2 portion of the trial is designed to evaluate the ORR plus the rate of patients with SD of at least 4 months duration of the RP2D (80 mg/m^2 of tinostamustine administered over 1 hour (± 5minutes) on Day 1 and 15 of each 4-week treatment cycle). Secondary objectives are evaluation of the safety and tolerability of the RP2D in selected solid tumor indications.

Phase 1: Dose Escalation until MAD (Complete):

In the Phase 1 portion of the trial, tinostamustine was escalated following the standard 3+3 design. The decision to escalate to the next dose level occurred after all patients in a given cohort completed Cycle 1 of treatment and were evaluated for safety and toxicity. A Safety Review Committee (SRC) that includes the Investigators and Sponsor/sponsor's representatives reviewed available data including toxicity and activity data to reach consensus on dose levels and determination of the MTD and RP2D. The dose escalation levels are defined in Section 3.2 and Table 2.

In the 3+3 design, if one of the 3 patients had a dose-limiting toxicity (DLT) (as defined below), the cohort was to be expanded to a maximum of 6 patients. If only 1 of the 6 patients had a DLT, dose escalation was to continue. If 2 patients had a DLT, dose escalation was to stop, regardless of the number of patients that had been treated in this cohort (e.g., if patients 1 and 4 had DLTs then patients 5 and 6 would not be treated). If 2 or more DLTs occurred in a 6-patient cohort, this dose was to be declared the MAD, and the prior dose level or an intermediate dose level was to be declared the MTD. The MTD was confirmed when 6 patients were treated at a dose level with less than 2 DLTs.

In Phase 1, the PK profiles of tinostamustine in plasma were assessed in each patient during the escalation phase, and in Phase 2, a minimum of 50 patients will participate in the PK analysis. Blood sampling will occur in Cycle 1 only at each drug administration.

The RP2D was defined by the Sponsor after all information on safety, toxicity and pharmacokinetics of the various dose levels and in respect of the underlying diseases was reviewed. The following data were considered for the selection of the respective RP2D to go forward to the Phase 2 portion of the protocol:

- DLTs and also all investigational product-related Grade 2 toxicities in all escalation cohorts;
- Dose-modifying events (DMEs): DMEs that were similar to DLTs but occur subsequent to Cycle 1;
- Maximum dose delivered per administration in a schedule and the related plasma C_{max} during infusion consistently delivering >1 µM of tinostamustine (parent compound); and
- Quality of response and duration of response in all escalation cohorts.

In October 2018, the SRC recommended 80 mg/m^2 administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle as the dose for Phase 2.

Phase 2: Evaluation of Response Rate in Selected Solid Tumor Cohorts

The Phase 2 portion of the trial is designed to determine the ORR plus the rate of patients with SD of at least 4 months duration of the RP2D (80 mg/m^2 of tinostamustine administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle).

The following cohorts will be opened to recruit patients.

- Cohort 1: Relapsed/refractory SCLC
- Cohort 2: Relapsed/refractory STS
- Cohort 3: Relapsed/refractory TNBC*
- Cohort 4: Relapsed/refractory ovarian cancer
- Cohort 5: Relapsed/refractory endometrial cancer*

**On 05 March 2021, following an evaluation of the development of EDO-S101 (Tinostamustine) across multiple studies, the Sponsor has taken the decision to halt recruitment into the Cohorts for relapsed/refractory triple-negative breast cancer (TNBC) and relapsed/refractory endometrial cancer on this study. This decision was made to enable focusing of resources into a defined and select set of patient cohorts.*

Each cohort will recruit 10 patients (stage 1) expanding to a possible 29 (stage 2) under a Simon 2-stage design[13], resulting in a total number of patients treated at 80 mg/m^2 administered over 1 hour (± 5 minutes) on Day 1 and 15 of each 4-week treatment cycle between 56 to 160 who will be monitored for safety and efficacy. In Phase 2 the PK profile of tinostamustine will be assessed in a minimum of 50 patients.

If there are no successes or only 1 success in the first 10 patients enrolled into each specific Phase 2 cohort, recruitment to that cohort will be stopped. Recruitment to stage 2 may continue while stage 1 is being evaluated, however, this is expected to be relatively few patients. If there are 2 or more successes in the first 10 patients enrolled in a given phase 2 cohort, an additional 19 patients will be treated for a total of 29. If it becomes clear that there will be 5 or fewer successes in a cohort of 29 patients, then the cohort will be stopped for lack of efficacy.

In each cohort, a success is defined as: CR or PR of any duration, or SD that persists for at least 4 months.

The Sponsor may suspend or discontinue enrollment to an expansion cohort at any time due to slow patient accrual rates or other reasonable cause.

Stopping Rules (Phase 1):

To ensure patients' safety, stopping rules were applied in the dose escalation phase. If 66% or more patients treated at any given time of the dose escalation part of the trial experienced the following Grade 2 toxicities, the trial was to be stopped for enrollment and the risk was to be assessed and addressed by the Sponsor.

- Grade 2 venous thrombosis
- Grade 2 increase of serum creatinine (>1.5 - 3.0 x upper limit of normal [ULN])
- Grade 2 nervous system disorders excluding headache

Treatment may continue until progression or intolerable toxicity up to a maximum of 12 cycles. Investigator and the Sponsor may decide to reduce a patient's dose in case of safety concerns. If

toxicity issues are resolved, the original dose can be administered at the next cycle. If the patient cannot tolerate the reduced dose, then the patient will be withdrawn from the study.

Radiologic response assessment by computed tomography scans will be performed at baseline and every 2 cycles. Tumor response will be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Section 13.3).

The duration of the Phase 2 portion of the trial is expected to be approximately 24 months for patient enrollment and treatment with 12 months of follow up for a total duration of 36 months.

5.2 Dose Escalation and Schedules

The dose levels, infusion time, and dosing frequency for each cohort of patients during dose escalation is summarized in Table 2.

Table 2 Dose Level, Infusion Time, and Dosing Frequency

Dose Level	Tinostamustine Dose	Administration	Schedule
-1*	40 mg/m^2	30 min infusion	D1 and D15 every 28 days
1 – Starting Dose	60 mg/m^2	30 min infusion	D1 and D15 every 28 days
2	80 mg/m^2	30 min infusion	D1 and D15 every 28 days
3	100 mg/m^2	30 min infusion	D1 and D15 every 28 days
4**	60 mg/m^2	60 min infusion	D1 and D15 every 28 days
5	80 mg/m^2	60 min infusion	D1 and D15 every 28 days
6***	100 mg/m^2	60 min infusion	D1 and D15 every 28 days

* If a patient experiences a DLT at dose level one (60 mg/m^2), tinostamustine will be reduced one dose level to 40 mg/m^2.
** If a patient experiences a DLT at the 60 mg/m^2, 60-minute infusion dose-level, tinostamustine will be reduced one dose level to 40 mg/m^2, 60 minutes infusion time.
*** Additional dose escalations will be considered until the MAD is reached.

The SRC and the Sponsor in agreement may increase the number of patients treated at a given pre-specified or intermediary dose level and dosing schedule to better define the safety profile of tinostamustine and enhance the clinical experience at each participating site. Dose levels may be expanded to include additional patients if such patients can be enrolled ≤ 14 days after the third (or sixth) patient was first dosed with tinostamustine in a given cohort.

During the trial, the SRC and Sponsor may have decided if additional or intermediary dose groups were to be opened at dose levels below the MAD to better define the MTD.

5.3 Definition of DLT

Toxicities will be assessed regarding type and severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, June 2010, with the exception that in Phase 2, assessment of QTc prolongations constituting AEs of special interest will be based on CTCAE version 5.0. Toxicity data will be collected for all patients throughout their time on trial.

DLTs were defined as:

- Hematologic DLTs
  - Grade 4 neutropenia lasting for 5 days or more;
  - Grade 3 or 4 neutropenia with fever ≥38.5C
  - Grade 3 thrombocytopenia with bleeding which requires platelets transfusion
  - Grade 4 thrombocytopenia
- Non-Hematologic DLTs
  - ≥Grade 3 nausea, vomiting that persists beyond 2 days despite administration of optimal supportive treatment.
  - ≥Grade 3 diarrhea that persists ≥2 days despite use of optimal anti-diarrheal treatments
  - Serum creatinine ≥3 x ULN
  - Bilirubin ≥3 x ULN
  - ≥Grade 3 ALT and AST in patients without liver metastases
  - ≥Grade 4 ALT and AST in patients with liver metastases
  - Other non-hematologic toxicities of ≥Grade 3, except for the following:
    - Adverse events related to the underlying disease
    - CTCAE Grade 3 fatigue
    - Alopecia
    - Isolated, asymptomatic elevations in biochemistry laboratory values lasting ≤7 days. This includes electrolyte abnormalities that respond to medical intervention
- Any toxicity resulting in a delay of the next dose (Cycle 2 Day 1) ≥14 days

If at any time during Phase 1 dose escalation a patient experienced a DLT, the trial treatment was to be stopped and the toxicity(ies) in question followed until resolution to CTCAE ≤Grade 1 or baseline. If the treating physician decided to re-initiate treatment, tinostamustine was to be reduced one dose level. Once a dose level reduction occurred, patients were required to remain at this reduced dose.

For dose escalation and determination of the MTD, only DLTs that occurred during the first cycle of treatment were to be considered in decisions regarding dose escalation. DLTs or other clinically

significant toxicities that occur after cycle 1 (dose modifying events) were taken into consideration when determining the RP2D.

Patients who experienced a non-laboratory, tinostamustine-related DLT were to be evaluated weekly until resolution to ≤Grade 1 or return to baseline and then monthly until return to baseline or stabilization of the event, whichever came first. For abnormal laboratory values that qualified as DLTs, patients were to be followed twice weekly until values return to ≤Grade 1 or baseline, whichever came first.

For the Phase 2 dose cohort expansion, a patient must meet the treatment criteria described in Section 8.6 to receive the next dose of therapy. The Investigator in consultation with the Sponsor may decide to reduce a patient's dose to 60 mg/m^2 in case of safety concerns. If toxicity issues are resolved, the original dose can be administered at the next cycle. If the patient cannot tolerate the reduced dose, then the patient will be withdrawn from the study.

5.4 Stopping Rules for Phase 2

Stopping rules in Phase 2 apply for patients who experience QTc prolongations >500 ms or change from baseline >60ms (Grade 3) that are not transient or occur in more than 1 treatment cycle.

If the QTcF value on the electrocardiogram (ECG) machine printout is >500 ms or represents an increase >60 ms from baseline, 2 additional ECGs are to be performed approximately 1 minute apart. If the average QTcF of the 3 ECGs is >500 ms or increased >60 ms from baseline, the tinostamustine infusion must be stopped. The patient should stay in the unit until the QTcF has decreased to baseline. In addition, the patient is to be continuously observed for syncope or other clinically relevant cardiac events.

A thorough evaluation of ECGs, including expedited central review of Grade 3 QTc prolongations by an independent assessor, will be performed. The decision will then be made by the Investigator in consultation with the Medical Monitor, whether tinostamustine treatment is to continue be postponed or stopped. **(**Refer to Section 8.7, Dose Modification Guidelines and Stopping Rules for Patients Who Experience Clinically Significant QTcF Prolongations).

6 SELECTION AND WITHDRAWAL OF PATIENTS

6.1 General Inclusion Criteria for Phase 1 and Phase 2 Portions of Trial

To be eligible for participation in the trial, patients must meet all of the following inclusion criteria:

- Patient willing and able to sign the informed consent.
- Patients age ≥18 years at signing of the informed consent.
- Life expectancy > 3 months.
- Histologically confirmed diagnosis of advanced or metastatic solid tumors, disease should have progressed during or following at least 1 previous line of therapy and no other standard therapy with proven clinical benefit is available or recommended based on the investigator's individual risk-benefit assessment for the patient.
- Patients with secondary metastasis to the central nervous system (CNS) are eligible if they have had brain metastases resected or have received radiation therapy ending at least 4 weeks prior to trial day 1 and they meet all of the following criteria:

  (1) Residual neurological symptoms ≤Grade 1.

  (2) No glucocorticoids requirement or patients may be receiving low doses of glucocorticoids providing the dose has been stable for at least 2 weeks prior to starting the trial medication (cf Section 7.14.1).

  (3) Follow-up imaging studies show no progression of treated lesions and no new lesions
- Evaluable disease; measurable on imaging as assessed by RECIST version 1.1.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2 (Section 13.1).
- Absolute neutrophil count (ANC) (polymorphonuclear [PMN] cells plus bands) >1,000/ µL.
- Platelets ≥100,000 / µL. Platelet transfusions within the 14 days before Day 1 of Cycle 1 is prohibited.
- Aspartate aminotransferase/alanine aminotransferase (AST/ALT) ≤3× ULN. In cases with liver involvement ALT/ AST ≤5× ULN.
- Total bilirubin ≤1.5 mg/dL unless elevated due to known Gilbert's syndrome.
- Creatinine ≤1.5 ULN.
- Serum potassium and magnesium at least at the lowest limit of normal (LLN), before every IMP administration. If it is below the LLN, supplementation is permissible.
- Female study participants of child-bearing potential and their partners, and male study participants who intend to be sexually active with a woman of child-bearing potential, must be willing to use at least TWO highly effective forms of contraception. This should start from the time of study enrollment and continue throughout IMP administration. For female study participants of child-bearing potential this must continue using contraception for at least six months after the last administration of the IMP. Female study participants should be willing to have a pregnancy test performed at screening, ≤ 1 day prior to day 1 of each IMP

administration and at study treatment discontinuation. Male study participants who are sexually active with a woman of child-bearing potential should also use a condom during treatment and for at least ninety (90) days after the last administration of IMP. Vasectomized males are considered fertile; therefore, vasectomized partners and patients must be willing to use a secondary method of effective birth control. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

6.2 Exclusion Criteria for Phase 1 and Phase 2 Portions of the Trial

To be eligible to participate in the trial, a patient cannot meet any of the following exclusion criteria:

- Patients with primary CNS cancer.
- Patients with QTc interval (Fridericia's formula) >450 ms.
- Patients who are on treatment with drugs known to prolong the QT/QTc interval. Refer to CredibleMeds list of drugs with known risk of Torsade des pointes (TdP): http://crediblemeds.org/new-drug-list.
- Patients who are being treated with valproic acid for any indication (epilepsy, mood disorder).
- Any serious medical condition that interferes with adherence to trial procedures.
- Prior history of another solid tumor malignancy diagnosed within the last 3 years of trial enrollment excluding adequately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or *in situ* cervical cancer, *in situ* breast cancer, *in situ* prostate cancer (patients must have shown no evidence of active disease for 2 years prior to enrollment).
- Pregnant or breastfeeding women.
- New York Heart Association (NYHA) stage III/IV congestive heart failure (Section 13.2). The following arrhythmias: atrial fibrillation/flutter with poor rate control, documented sustained ventricular tachycardia (defined as >30 seconds or requiring cardioversion before 30 seconds have elapsed) or TdP.
- Significant co-morbidities (e.g., active infection requiring systemic therapy, history of human immunodeficiency virus [HIV] infection, or active Hepatitis B or Hepatitis C).
- Use of other investigational agents or previous anticancer therapies within 28 days prior to the first dose of tinostamustine, provided the patient has recovered from any related toxicities ≥Grade 1.
- Steroid treatment within 7 days prior to trial treatment. Patients that require intermittent use of bronchodilators, topical steroids, or local steroid injections will not be excluded from the trial. Patients who have been stabilized to 10 mg prednisolone orally (PO) once daily (QD) (or equivalent), daily (or less) at least 7 days prior to IMP administration are allowed.

6.3 Phase 2 Evaluation of Toxicity and Response Rate in Selected Solid Tumours;

Specific Eligibility Criteria

Phase 2 patients must meet the cohort-specific inclusion/exclusion criteria in addition to the general inclusion/exclusion criteria for Phase 1 and Phase 2 trial listed above.

Confirmation of the availability of a tumor sample from the primary or recurrent cancer must be provided (archival samples are acceptable).

6.3.1 Cohort 1 Patient Population: Relapsed/Refractory Small-cell Lung Cancer (SCLC)

1. Histologically or cytologically confirmed limited or extensive disease stage of SCLC.
2. Must have received at least 1 line of prior combination chemotherapy or biological therapy and no other standard therapy with proven clinical benefit is available or recommended based on the investigator's individual risk-benefit assessment for the patient.
3. At least 28 days should have elapsed since prior treatment as long as the patient has recovered from any related toxicities to ≤ Grade 1 (or ≤ Grade 2 for any symptomatic neuropathy or endocrinopathies).
4. Prior radiotherapy is acceptable provided the patient has recovered from any radiotherapy related acute toxicities.
5. The disease should be progressing during or relapsing after the previous treatment.
6. Presence of measurable disease as defined by RECIST version 1.1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

6.3.2 Cohort 2 Patient Population: Relapsed/Refractory Soft Tissue Sarcoma

1. Histologically confirmed diagnosis of advanced, unresectable, or metastatic STS not amenable to curative treatment with surgery or radiotherapy excluding: neuroblastoma, GIST, embryonal rhabdomyosarcoma, Kaposi sarcoma, chondrosarcoma, osteosarcoma or Ewing's sarcoma.
2. Must have received at least 1 prior line chemotherapy or biological therapy regimen and no other standard therapy with proven clinical benefit is available or recommended based on the investigator's individual risk-benefit assessment for the patient. At least 28 days should have elapsed since prior chemotherapy, as long as the patient recovered from any related toxicities to ≤ Grade 1 (or ≤Grade 2 for any symptomatic neuropathy or endocrinopathies).
3. The disease should be progressing during or relapsing after the previous treatment.
4. Presence of measurable disease as defined by RECIST version 1.1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

6.3.3 Cohort 3 Patient Population: Relapsed/Refractory Triple Negative Breast Cancer

RECRUITMENT INTO THIS COHORT HAS NOW BEEN HALTED

6.3.4 Cohort 4 Patient Population: Relapsed/Refractory Ovarian Cancer

1. Histologically or cytologically confirmed advanced ovarian cancer: epithelial ovarian cancer, including primary peritoneal cancer or fallopian tube cancer (excluding borderline ovarian cancer, MMMT) of high grade serous histology, or high grade endometrioid cancer, that is resistant or refractory to platinum therapy and no other standard therapy with proven clinical benefit is available or recommended based on the investigator's individual risk-benefit assessment for the patient. Clear cell carcinomas are excluded.

   Patients with primary platinum refractory disease (failure to respond to initial platinum treatment or relapse within 4 weeks) and patients with primary platinum resistant disease (progression within 6 months of completing first line platinum-based therapy) are excluded from the study.

2. At least 28 days should have elapsed since prior chemotherapy as long as the patient recovered from acute toxicity of previous therapies to ≤ Grade 1 (or ≤ Grade 2 for any symptomatic neuropathy or endocrinopathies).
3. The disease should be progressing during or relapsing after the previous treatment.
4. Presence of measurable disease as defined by RECIST version 1.1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

6.3.5 Cohort 5 Patient Population: Relapsed/Refractory Endometrial Cancer

RECRUITMENT INTO THIS COHORT HAS NOW BEEN HALTED.

6.3.6 Withdrawal of Patient from Trial Treatment

Patients can withdraw from the trial at any time without giving any reason if they wish to do so without any consequences for their further medical treatment. The investigator can decide to withdraw a patient from the trial for urgent medical reasons. Furthermore, patients will need to be discontinued from further trial treatment in the event of any of the following:

- Unmanageable toxicity.
- Pregnancy.
- Physician decision if continuation is not in the patient's best interest.
- Termination of the trial by the Sponsor.
- Other reasons (e.g., major protocol violation, non-compliance).
- Progressive disease.

If a patient is withdrawn from the trial, the primary reason must be recorded in the electronic case report form (eCRF) and the Investigator should make every effort to perform the assessments listed in the Schedule of Assessments (Table 1) under the Investigational product Discontinuation column (at any time or Day 28 of the last treatment cycle).

Patients who are withdrawn prior to receiving

6.3.7 Early Trial Termination

The Sponsor has the right to close a trial site, the trial or an expansion cohort at any time. Whenever possible, mutual consultation between the Sponsor and the Investigators should occur before a final decision. Events that may trigger early trial termination include, but are not limited to:

- Initial dose level exceeds the MTD or other toxicity finding (Stage 1 only).
- Change in development plans for the investigational product.
- Slow recruitment.

If based on continuous safety monitoring across the development program, the benefit-risk ratio for the use of the investigational product would become negative, the Sponsor will decide about discontinuation of the development program in parts or in its entirety.

The Sponsor will notify the accredited Institutional Review Board (IRB)/Independent Ethics Committee (IEC) as well as the applicable competent authorities without undue delay of a temporary halt and early termination including the reason for such an action. The investigator will ensure that all patients are kept informed.

7 TRIAL ASSESSMENTS

A tabular schedule of evaluations and procedures is provided in Table 1 (Schedule of Assessments).

7.1 Screening

The Investigator at each trial site is responsible for maintaining a record of all patients screened, including both those who enter the trial and those who are excluded. Screening procedures will be performed no more than 28 days prior to baseline, with the exception for scans that will be performed no more than 28 days prior to baseline (with 7-day window i.e., scans performed no more than 35 days prior to baseline will be accepted). The baseline is defined as the first day on which investigational product is administered. Screening procedures are listed in Table 1 (Schedule of Assessments).

7.2 Informed Consent

Each potential patient must sign a written ICF prior to performing any trial specific procedures. A copy of the signed informed consent form will be provided to the patient. Separate consent must be provided for collection of samples for determination of gene expression.

7.3 Inclusion/Exclusion Criteria and Patient Treatment Assignment

Inclusion and exclusion criteria will be reviewed for each potential patient during Screening. All eligible patients will be treated with tinostamustine employing sequential enrollment (i.e. as they qualify for participation). In the first phase of the trial (Phase 1), the dose received for each eligible patient was dependent on the requirements of the dose escalation scheme at the time the patient was enrolled. In the second phase of the trial (Phase 2), all patients will be treated with the tinostamustine at 80 mg/m^2 administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle.

7.4 Demographics and Medical History

Each patient's medical history will be documented at Screening, including demographic information, relevant medical history, current primary cancer diagnosis, and prior cancer treatments (chemotherapies and immunotherapies, radiation therapy, surgeries, etc.).

7.5 Physical Examination

A complete physical examination will be performed at Screening, at Day 1 of each cycle and at the time of investigational product discontinuation (at any time or Day 28 of the last treatment cycle). On Day 15 and Day 22, abbreviated physical examination directed by disease site and symptoms will be performed. The abbreviated physical examination includes vitals and ECOG performance status.

The findings of each examination will be recorded on the source documents and in the eCRF. The complete physical examination will include:

- General appearance
- Head, eyes, ears, nose, and throat
- Respiratory
- Cardiovascular

- Musculoskeletal
- Abdomen
- Neurologic
- Extremities
- Dermatologic
- Lymphatics

Interim or symptom-directed physical examinations will be performed at other times, if necessary, at the discretion of the Investigator to evaluate potential adverse events or clinical laboratory abnormalities.

7.6 Vital Signs, Height and Weight

Vital signs will include resting supine blood pressure, pulse, respiratory rate, and temperature. Vital sign determinations will be performed at Screening, Days 1, 15 and 22. On each treatment day blood pressure, pulse, and respiratory rate will be recorded pre-dose, 3 hours (±10 minutes), and 6 hours (±10 minutes) from the start of the tinostamustine infusion, and at the time of investigational product discontinuation (at any time or Day 28 of the last treatment cycle). Due to the burden on the patients, after Cycle 1 the vitals for the 3- and 6-hour time points are considered optional assessments and should be done at the Investigator's discretion. If the 3- and 6-hour time points are not done, the Investigator must provide adequate instruction to the patient regarding potential allergic reactions, and this should be clearly documented in the patient chart.

Temperature will be recorded at pre-dose on each treatment day. Height will be measured at Screening or baseline only. Weight will be measured at Screening and in conjunction with vital sign determinations at Day 1 of each treatment cycle. The weight measured on Day 1 of each cycle will be used for investigational product calculations of body surface area (BSA). BSA will be calculated using the same formula for each patient at the site. The DuBois formula will be used to calculate the BSA.

7.7 ECOG Performance Status

ECOG performance status of each patient will be assessed at Screening and at every visit when a physical exam is performed including the time of investigational medicinal product discontinuation (at any time or Day 28 of the last treatment cycle) using the criteria provided in Section 13.1.

7.8 12-Lead ECG (Safety and Holter)

All ECGs will be obtained digitally using a Global Instrumentation (Manlius, NY, USA) M12R ECG and are to be performed after the patient is supine for 10 minutes.

A triplicate ECG will be performed during Screening (at least 1-2 minutes between each measurement) to determine patient eligibility for the trial and will be reviewed centrally.

During tinostamustine treatment, 2 types of ECGs are to be performed: Holter and safety ECGs.

Holter ECGs are stored continuously on a digital medium and will not be available for review until the data is received by ERT and analyzed (Section 7.8.1.1). Holter ECG readings will be used for the

final data analysis from selected predetermined time points as detailed below and will be read centrally using a high-resolution manual on-screen caliper semiautomatic method with annotations.

Safety ECGs (standard digital 12-lead) will be immediately available to site staff for assessment (Section 7.8.1.2).

7.8.1.1 Holter ECGs

Holter monitoring will commence 60 minutes prior to the start of tinostamustine infusion on C1D1 and 15 minutes prior to the start of tinostamustine infusion in C1D15 and will continue through 24 hours from the start of infusion.

Replicate 10 second, 12-lead ECGs will be extracted from the continuous recording at each of the following time points on C1D1 and C1D15:

- C1D1: -45, -30, -15 minutes pre-dose, and 15, 30, 45, 60, 75, 90, 120, 180, 360 minutes and 24 hours from the start of tinostamustine infusion.
- C1D15: prior to the start of infusion, and 15, 30, 45, 60, 75, 90, 120, 180, 360 minutes and 24 hours from the start of infusion.

The central reader interpretation of ECGs extracted from Holter monitoring will be used to determine all ECG data for trial endpoints including baseline QTcF interval for cardiac safety analyses.

7.8.1.2 Safety ECGs

A triplicate ECG is to be performed before tinostamustine administration on D1 (i.e., day of tinostamustine dosing) in each cycle. Furthermore, patients are to have single ECGs performed at 30 minutes (+/- 5min) and triplicate ECGs at 60 minutes (+/- 5 min) from the start of tinostamustine administration on D1 and D15 of each treatment cycle and a single ECG on D28 (±2 days) of last treatment cycle, at the end of study visit.

Expedited central reading of safety ECGs will be requested in all cases of Grade 3 or higher QTcF prolongations that occur within 6 hours from start of infusion. The results of the expedited central review will be made available to the site within 6 hours.

The Investigator's interpretation of ECGs will be used for patient safety management during the trial. For SAE reporting: initial assessment and reporting will be based on the local reading of the safety ECG and may be corrected if not confirmed by central reading.

7.9 Pharmacodynamics (Gene Expression)

Patient participation in the gene expression analysis is not mandatory for enrollment into the trial. Information on the purpose of genetic research in the gene-expression sub-trial is provided, either in the main ICF or a separate ICF, based on applicable regulatory requirements, to allow the patient to decide whether he or she want to participate in this part of the trial. Participation in this genetic research is voluntary.

If the patient agrees to participate in the gene expression analysis, a fresh or archival tissue sample will be collected during Screening. Formalin fixed paraffin embedded (FFPE) biopsy samples will be used. The Affymetrix chip technology for analyzing total ribonucleic acid (RNA) will be used. For formalin fixed paraffin embedded samples, RecoverAll method from Ambion® for isolating total RNA will be used. The isolated RNA is total RNA and will contain both messenger RNA (mRNA) and micro

RNA (miRNA). The expression profile will be analyzed for correlation with response or resistance to therapy. Details of sample preparation and shipping are described in the Laboratory Manual.

Samples will be stored in accordance with the IRB/IEC approved ICF and applicable laws. Several steps will be taken to keep the patient's identity and the genetic test result confidential throughout the trial (e.g., double coding of the samples; restricted access to the samples and testing results).

7.10 Clinical Laboratory Tests (Hematology, Chemistry and Urinalysis)

Certified local laboratories will perform all clinical laboratory tests and results will be provided to the Investigator. Blood samples for hematology determinations will be collected at Screening, Days 1 (- 2 days), 15 (- 2 days) and 22 (+/- 2 days) of treatment cycle 1 to the last treatment cycle, and at the time of investigational product discontinuation (at any time or Day 28 of the last treatment cycle). On tinostamustine administration days, blood samples for laboratory tests are to be collected and reviewed by the investigator before the start of tinostamustine infusion. Serum potassium and magnesium should be at least at the LLN before the start of tinostamustine infusion. If it is below LLN, they would need to be corrected and rechecked before the infusion proceeds. Hematology tests will include white blood cell count (WBC) plus differential, red blood cell count (RBC), hemoglobin, hematocrit, platelets and an ANC determination.

Blood samples for serum chemistry determinations will be collected at Screening, Day 1 and 15 of each treatment cycle, and at the time of investigational product discontinuation (at any time or Day 28 of the last treatment cycle).

On days of drug administrations, blood samples for hematology and serum chemistry determinations will be collected prior to administration of the investigational product. Additional samples can be collected, and determinations performed if clinically indicated.

Blood chemistry tests will include albumin, total protein, creatinine, uric acid, blood urea nitrogen, sodium, potassium, magnesium, calcium, glucose, total bilirubin, alkaline phosphatase, AST, ALT, gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and C-reactive protein (CRP). In addition, an evaluation of potassium and magnesium levels at screening and before every tinostamustine infusion will be performed and if lower than normal this would need to be corrected before the infusion proceeds.

Urine for routine urinalysis will be collected at Screening and at the time of investigational product discontinuation (at any time or Day 28 of the last treatment cycle). Urine microscopic examination will be performed if there are any positive findings upon dipstick assessment.

In the event of a clinically significant laboratory toxicity that is greater than or equal to Grade 2, more frequent laboratory tests should be performed until resolution or stabilization to less than or equal to Grade 1.

7.11 Pregnancy Testing and Contraception

A serum or urine pregnancy test will be performed for female patients of child-bearing potential at Screening on day -1 of each treatment cycle (prior to tinostamustine administration), and at the time of discontinuation of tinostamustine administration. The test results at Screening and D1 must be negative for the patient to be enrolled in the trial. A positive urine pregnancy test result observed following enrollment should be confirmed with a repeat serum pregnancy test and if confirmed positive, the patient must be withdrawn from treatment immediately. See Section 9.6.5 for details

regarding the pregnancy reporting procedure. A woman of child-bearing potential is defined as a female who does not meet the criteria for “Women Not of Childbearing Potential”: women ≥55 years of age and 12 consecutive months without menstrual bleeding or <55 years of age after surgical sterilization. Female study participants of child-bearing potential and their partners, and male study participants who intend to be sexually active with a woman of child-bearing potential, must be willing to use at least TWO highly effective forms of contraception from the time of study enrollment and continue throughout tinostamustine administration. For female study participants of child-bearing potential this must continue using contraception for at least six months after the last administration of the IMP. Male study participants who are sexually active with a woman of child-bearing potential should also use a condom during treatment and for at least ninety (90) days after the last administration of IMP.

Vasectomized males are considered fertile; therefore, vasectomized partners and patients must be willing to use a secondary method of effective birth control. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

7.12 Adverse Events (AEs)

Monitoring and recording of AEs will be conducted from the time of ICF signature to point of discontinuation of tinostamustine (D28 of last treatment cycle). AEs, including serious adverse events (SAEs), will be captured in the eCRFs from the time of ICF signature through to point of discontinuation of tinostamustine. Only AEs ongoing at Tinostamustine Discontinuation Visit are required to be followed to resolution or stabilization. In the event of a clinically significant laboratory toxicity that is ≥Grade 2, more frequent laboratory tests should be performed until resolution to Grade 1 or stabilization (i.e., the CTCAE grade remains the same for at least 14 days). The final resolution/stabilization date is recorded in the AE eCRF. During Follow-up, any new SAE commencing within 30 days of Tinostamustine Discontinuation Visit should be recorded and followed to resolution.

7.13 Infusion Site and Allergic Reaction Assessment

All injection site reactions will be considered AEs. However, the nature and severity of each injection site reaction will be determined using the CTCAE criteria, version 4.03 (June 2010) in Phase 2.

In Phase 2, a 2 mg/mL tinostamustine infusion solution after reconstitution will be utilized. Assessment of injection site reactions must be performed on each treatment day at pre-dose and at the end of infusion. Additional evaluation must be performed at 1-hour (± 15 minutes) post dose in patients who present signs and symptoms of injection site reactions at the end of infusion. (See Section 8.10 for possible infusion reactions). The Investigator must provide adequate instruction to the patient regarding potential allergic reactions, and this should be clearly documented in the patient chart.

7.14 Prohibited Concomitant Medications and Procedures

7.14.1 Steroids

Use of bronchodilators, topical steroids, or local steroid injections will only be allowed for patients who require intermittent therapy. Treatment with steroids will be allowed for patients who have been stabilized to oral daily administration of prednisone 10 mg PO QD (or equivalent) or less, 7 days prior to tinostamustine administration, (except for patients with secondary metastasis to CNS disease as permitted in the inclusion criteria Section 6.1 and patients with rash and/or allergic reactions as permitted in Section 8.9)

7.14.2 Valproic Acid

Patients receiving valproic acid for any indication (epilepsy, mood disorder) must be excluded from the trial.

7.14.3 Allopurinol

Pre-treatment with allopurinol is contraindicated. There may be increased risk of severe skin toxicity when tinostamustine and allopurinol are administered concomitantly. As prevention in patients with high risk for developing tumor lysis syndrome (TLS) or for the treatment of established TLS, patients should receive rasburicase.

7.14.4 Serotonin 5-HT3 receptor antagonists

Palonosetron (Aloxi®) is the only serotonin 5-HT3 receptor antagonist that does not cause significant QTc changes; therefore, if required, it could be used for antiemetic prevention.

Ondansetron (Zofran®) is associated with QTc prolongation and cardiac arrhythmias, with a dose related effect. Consequently, it is contraindicated during the administration of tinostamustine. Given the short half-life of tinostamustine, ondansetron can be used, if needed, for the prophylaxis of delayed nausea and vomiting. A minimal interval of 24 hours should be respected between the last intake of ondansetron and the next tinostamustine infusion. This is related to the half-life of 4-6 hours of ondansetron. This interval should be extended to 48 hours in patients with mild biological hepatic impairment but who are still eligible (see inclusion and exclusion criteria). In this category of patients, a significant prolongation of ondansetron's half-life has been reported.

7.14.5 NK1 receptor antagonists

Aprepitant (Emend®) is not allowed, since interactions with alkylating agents have been demonstrated. Aprepitant has additional interactions that could lead to an increase of side effects or decrease in efficacy of tinostamustine.

7.14.6 Investigational agents

Use of other anti-cancer investigational agents within 28 days prior to the first dose of tinostamustine provided the patient has recovered from any related toxicities ≥Grade 1.

Use of any other investigational medicinal product or non-approved experimental therapy is not allowed.

7.15 Efficacy Evaluations

7.15.1 Baseline Disease Assessment

Baseline (Screening Visit) tumor assessments will be performed using CT scan. Patients will have a baseline tumor assessment done within the 28 days (+7-day window) prior to Cycle 1, Day 1.

7.15.2 Disease Response Assessments

Radiologic response assessment by computed tomography (CT) or magnetic resonance imaging (MRI) will be performed at baseline and every 2 cycles. Tumor response will be evaluated according to RECIST version 1.1 (Section 13.3).

7.15.3 Follow-up Assessments

PFS Response Follow-up

Patients who have discontinued trial treatment for reasons other than PD will be assessed per RECIST 1.1 every 8 weeks (± 2 weeks) until documentation of PD or the initiation of a subsequent anti-cancer therapy, whichever comes first.

Survival Follow-up

Patients will be contacted every 3 to 4 months for the subsequent use of anti-cancer therapy as well as survival until 1 year after the last patient's first treatment (C1D1).

7.16 PK Assessments

Plasma samples will be collected for determination of tinostamustine concentrations as well as its 2 metabolites, M2 and M8, using a method fully validated according to the relevant guidelines. The PK profile of tinostamustine, M2 and M8 in plasma will be assessed by analyzing parameters such as C_{max}, AUC, and time to maximum concentration (T_{max}), and elimination half-life at each drug administration of Cycle 1 in each patient during the dose escalation and in Phase 2 a minimum of 50 patients will participate in the PK analysis. The blood sampling schedule for the PK assessment is conducted in Cycle 1 only on Day 1 and 15 during tinostamustine administration. Samples are taken as follows: up to 0.5 hours prior to dose administration and at 15, 30 and 45 minutes, 1 hour, 75 and 90 minutes, and 2, 3, 6, and 24 hours from the start of the tinostamustine infusion.

The following time windows are permissible for all PK blood draws:

Sampling Time	Time from Scheduled Sampling Allowed
From > 0 up to ≤ 90minutes from the start of tinostamustine infusion except for 60min.	± 5 minutes
At 60 minutes from the start of tinostamustine infusion	- 5 minutes but as close to the calculated end of the IMP infusion as possible and before the end of IMP infusion
From > 2 hours to 6 hours from the start of tinostamustine infusion	± 10 minutes

At 24 hours from the start of tinostamustine infusion	± 2 hours

Timings may need to be adjusted to allow for the infusion technique (priming of the line). Any change must be documented (following discussion with the Sponsor) for each patient by the site.

The PK assessments together with the ECG Holter results will be used to perform a concentration QTc-analysis following a separate statistical analysis plan (SAP).

7.17 Missed Visits

If a patient misses a scheduled visit to the trial site, the patient will continue on protocol and attend the next scheduled visit. In this case, the treating medical team should at least contact the patient by phone to establish patient status. If a patient misses 2 scheduled visits, his or her continued trial participation will be re-evaluated for possible non-compliance.

8 TRIAL TREATMENT

8.1 Investigational Medicinal Product Description

Other Names: tinostamustine is the International Nonproprietary Name (INN) of the Investigational Medicinal Product. Tinostamustine is a first in class alkylating HDACi fusion molecule that is being investigated for the treatment of relapsed/refractory hematologic malignancies and advanced solid tumors. The active pharmaceutical ingredient is insoluble in water and having its optimal solubility in an acidic medium. The drug substance is sensitive to degradation at pH values below 4.5 and precipitates in blood at pH 7. In addition, it rapidly hydrolyses in water and is sensitive to ambient temperature. The chemical structure of tinostamustine is comprised of 3 chemical moieties that include a DNA alkylation moiety, a purine- like benzimidazole ring and a histone-deacetylase inhibiting moiety.

8.2 Storage and Dispensing

Tinostamustine should be stored at 2 to 8°C in a secure area with access limited to the Investigator and authorized site staff. Before administration each vial tinostamustine needs to be reconstituted with 20 mL of 0.9% saline and the solution must be further diluted with 0.9% saline to a total volume of 50mL. The diluted solution is stored in infusion container (bottle or bag) for a maximum of 10 hours, of which a maximum of 4 hours may be at room temperature, with the remaining storage period at 2-8°C. The storage period at room temperature must include the infusion duration of 1 hour Tinostamustine is compatible with infusion materials indicated in the Pharmacy Manual.

Only patients enrolled in the trial may receive investigational product. At Day 1 and Day 15 of each 4-week treatment cycle, the single dose of tinostamustine is to be dispensed only by the Principal Investigator (PI), sub-Investigators, or authorized personnel at the institution(s) specified on the US Food and Drug Administration (FDA) Form 1572 (relevant for USA) and listed on the delegation of authority log.

Under no circumstances is the investigational drug to be used other than as directed within this trial protocol.

8.3 Supply, Packaging and Labeling

Tinostamustine is provided as a lyophilized powder in single dose, sealed glass vials. Each 50 mL vial will contain 100 mg tinostamustine. Hydroxyl-propyl-β-cyclodextrin (HPβCD) is present as the main functional excipient to keep the drug in solution at physiological pH after reconstitution. The vials are of clear glass Type I and stopper (V10 F597 W4432/50 WESTAR RS, Westar Pharmaceuticals Services) as well as Aluminum flip-off cap (20 mm, Westar Pharmaceuticals Services) to ensure container closure. All materials are in conformance with United States Pharmacopeia (USP) and Pharmacopoea Europaea (Ph. Eur.).

8.4 Treatment Allocation

Trial number allocation and dosing cohort assignment for eligible patients will be completed according to a process defined by the Sponsor.

8.5 Investigational Medicinal Product Administration

Following Screening, all patients who were eligible to participate in the first phase of the trial (Phase 1) were assigned to a dosing cohort and receive a single dose of tinostamustine at the beginning of each treatment cycle. The investigational product (reconstituted and diluted solution as described in Section 8.2) was administered by i.v. infusion through a peripheral vein or port over a 30-minute infusion time for the first 3 dose levels (See Table 2). Starting at the fourth dosing cohort (See Table 2), the investigational product was administered by i.v. infusion through a peripheral vein or port over a 60-minute infusion time. **For Phase 2, the dose is 80 mg/m^2 administered over 1 hour (± 5 minutes) on Day 1 and 15 of each 4-week treatment cycle.**

The timing of the IMP infusion is affected by whether the iv line is pre-filled with saline or IMP:

- If the iv line is pre-filled with saline, the start of actual IMP administration will be delayed until the saline is flushed through, and the end of the IMP infusion will be delayed by the same period of time as the last of the IMP is flushed through.
- If the line is pre-filled with IMP, then the start of the IMP administration will occur at the start of the infusion, and the IMP infusion will finish after 60 minutes when the IMP is flushed from the line.

Instructions for preparation of each dose of investigational product during each phase of the trial are provided in the Pharmacy Manual. The PI or qualified site personnel will administer tinostamustine by i.v. infusion.

Preparation and dispensing of the investigational product will be handled by the investigational site pharmacy. Instructions for safe handling of the investigational product are provided in the Pharmacy Manual. The requirements for maintaining drug accountability are provided in Section 8.8 of this protocol.

8.6 Treatment Criteria Beyond Cycle 1, Day 1

For a patient to receive the next dose of tinostamustine, the following criteria must be met:

- No active infection
- ANC ≥1,000/ µL
- platelets ≥ 100,000/ µL or >65% of platelet baseline level (whichever is higher). Baseline for D15 is the level of platelets before tinostamustine administration on D1 of the same cycle. Baseline for D1 administration is the level of platelets on D1 of the previous treatment cycle.
- non-hematologic treatment-related toxicities have improved to ≤Grade 1 or to the patient's baseline values (except alopecia).

In the event of toxicity leading to dose delay, tinostamustine dose will be reduced to 60 mg/m2. If toxicity issues are resolved, the original dose can be administered at the next cycle, investigator's discretion.

If a patient does not meet these criteria, next dosing will be delayed by up to 14 days and the patient should be evaluated within 48-72 hours. If the next administration is delayed by more than 14 days, the investigator will determine if there is clinical benefit for patient to continue treatment when the

patient's toxicity returns to Grade 1 or the patient's pre-event baseline. The medical monitor must be informed of any treatment delay (email: EDOS101-medical-monitor@mundipharma-rd.eu).

8.7 Dose Modification Guidelines and Stopping Rules for Patients Who Experience Clinically Significant QTcF Prolongations

If the QTcF value on the ECG machine printout is >500 ms or represents an increase >60 ms from baseline, 2 additional ECGs are to be performed approximately 1 minute apart. If the average QTcF of the 3 ECGs is >500 ms or increased >60 ms from baseline, the tinostamustine infusion must be stopped. Remove the infusion bag to ensure that the infusion is stopped. The patient should stay in the unit until the QTcF has decreased to baseline. In addition, the patient is to be continuously observed for syncope or other clinically relevant cardiac events.

A thorough evaluation of ECGs, including the expedited central reading of Grade 3 QTc prolongations, needs to be performed. The decision will then be made by the investigator in accordance with the Sponsor, whether administration of tinostamustine can continue or whether administration of tinostamustine is to be postponed.

As a general rule:

- Administration of ≥50% of the planned dose will be considered as a full dose.
- If less than 50% of the planned dose was administered, the remainder to a full planned dose can be administered on the following day.
  - If the centrally reviewed QTcF value confirms the local finding and is >500 ms or increased >60 ms from baseline, subsequent doses should be reduced.
  - If a centrally confirmed QTc prolongation (>500 ms or increased >60 ms from baseline) occurs again with the reduced dose, the patient will be taken off trial treatment.
  - If the QTc prolongation is not confirmed by a central assessor, meaning a central read of ≤500 ms or increased ≤60 ms from baseline, the patient can continue the treatment with the initially planned dose within the judgement of the investigator.

Summary Guidance:

If centrally reviewed QTcF value confirms local measurement of >500ms or increase >60 ms from baseline (Grade 3)	1st occurrence: Reduce dose to 60 mg/m^2 for subsequent doses
If centrally reviewed QTcF value confirms local measurement of >500ms or increase >60 ms from baseline	2nd occurrence: Investigational treatment should be discontinued
If centrally reviewed QTcF does not confirm local measurement of > 500 ms or increased >60 ms from baseline	Investigational treatment can continue as planned according investigator's judgement

8.8 Investigational Medicinal Product Accountability

Investigational drug accountability records will be maintained throughout the course of the trial. The Investigator or designee will document the amount of tinostamustine received, the amount dispensed to trial patients and the amount destroyed locally.

Unused tinostamustine remaining at the completion of the trial will be destroyed at the site per institutional standard operating procedures, provided that destruction is documented. Destruction of drug supplies will take place only when drug accountability has been completed and the Sponsor/Contract Research Organization (CRO) has given written approval for destruction.

8.9 Supportive Care

Unless otherwise prohibited (see Section 7.14), supportive therapy for optimal medical care may be administered per institutional standard of care at the trial centers. Such supportive therapies may include but are not limited to:

1. For neutropenia: Growth factor support was allowed in Cycle 1 only beyond Day 7 in Phase 1 only. There were no restrictions for subsequent cycles. In Phase 2 Growth factor support is allowed per institutional standards.
2. For diarrhea: Appropriate treatment is allowed, e.g. loperamide, atropine-diphenoxylate, or octreotide.
3. For nausea and/or vomiting, see guidelines in Section 7.14.4.
4. For rash and/or allergic reactions: Steroids like hydrocortisone, dexamethasone, and antihistamines.

8.10 Drug Interactions/Precautions

As a precaution, patients who are on treatment with drugs known to prolong QT/QTc interval and those who have QTc interval longer than 450 ms are excluded. The most current list of drugs with known risk of TdP issued by Credible Meds: https://crediblemeds.org/new-drug-list should be reviewed by the Investigator (or delegated site staff) prior to dosing a patient . Precautions of use of the 5HT3 receptor antagonists are discussed in Section 7.14.4.

- Tinostamustine is a molecule composed of an alkylating moiety similar to bendamustine and a histone- deacetylase inhibiting moiety similar to vorinostat. Based on the clinical experience with these 2 agents, potential toxicities that may be seen with tinostamustine include some of the more common toxicities outlined below in addition to other, rare but serious toxicities such as TLS seen with bendamustine and thromboembolism observed with vorinostat.
- TLS was reported in patients with a large tumor burden. Onset typically occurs within the first treatment cycle with chemotherapeutic agent and, without intervention may lead to acute renal failure and death. Preventive measures include vigorous hydration and close monitoring of blood chemistry. Pretreatment with allopurinol as co-administration with alkylating agents is contraindicated as it increases the likelihood of mild to severe skin toxicity. Skin reactions including rash, toxic skin reactions and bullous exanthema. Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN), some fatal, have been reported when chemotherapeutic agents were administered concomitantly with allopurinol and other medications known to cause these syndromes. Patients with skin reactions must be closely

monitored. If skin reactions are severe or progressive treatment must be discontinued. Rasburicase is recommended instead of allopurinol.

- Patients treated with many alkylating agents are at risk for reactivation of infections including (but not limited to) hepatitis B, cytomegalovirus, Mycobacterium tuberculosis, and herpes zoster. Patients should undergo appropriate measures (including clinical and laboratory monitoring, prophylaxis, and treatment) for infection and infection reactivation prior to administration.
- The most common serious drug-related adverse reactions associated with HDAC inhibitors were pulmonary embolism and anemia. Physicians should be alerted to the signs and symptoms of these events, particularly in patients with a prior history of thromboembolic events.
- Hyperglycemia has been observed in association with HDAC inhibitors treatment.; therefore, serum glucose should be monitored, especially in diabetic or potentially diabetic patients. Adjustment of diet and/or therapy for increased glucose may be necessary.
- Infusion reactions (hypersensitivity) to alkylating agents may be immediate /or delayed. Symptoms include fever, chills, pruritus, and rash. In rare instances severe anaphylactic and anaphylactoid reactions.occurred. Assessment of infusion site reactions must be performed on each treatment day at pre-dose, 1 hr (±15 minutes). The patient will be observed at 1 hr (± 15 minutes post-dose) for potential allergic reactions (See Section 8.10 for possible infusion reactions).

  The Investigator must provide adequate instruction to the patient regarding potential allergic reactions, and this should be clearly documented in the patient chart.

  Allergic reactions during or shortly after the infusion may cause skin itching, rash, reddening of the skin, swelling of the face, hands, feet, shortness of breath or anaphylactic reactions. These reactions are generally transient and disappear after symptomatic treatment is applied. Patients should be carefully monitored for all reactions after the infusions and take appropriate prophylactic measures with corticosteroids and/or antihistamines to prevent such or more severe reactions in subsequent treatment cycles.

8.11 Overdose

Investigational product will be administered by the Investigator or qualified site personnel. Therefore, it is highly unlikely that an overdose will occur. However, in the event of an investigational product overdose due to pharmacy error, the PI and Sponsor/Sponsor's designee should be immediately notified and, if signs or symptoms are present the overdose recorded as an AE. The patient should be carefully monitored for potential adverse reactions and symptomatic treatment instituted as per institutional standards of care.

9 AES AND SAES

9.1 Definition of Adverse Event (AE)

An AE is any untoward medical occurrence associated with the use of a drugs in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug from any route of administration, formulation, or dose, including an overdose.

AEs also include:

- A new disease or exacerbation of a pre-existing disease e.g., increase in frequency or worsening in nature.
- Any deterioration in measurements of laboratory values or other clinical tests (e.g., ECG, vital signs or X-ray) that results in symptoms, a change in treatment, or discontinuation from tinostamustine.
- Other medical events regardless of their relationship to tinostamustine, such as accidents, falls and any injuries resulting from them.

AEs do not include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE.
- Pre-existing diseases or conditions present or detected at the start of the trial that do not worsen in severity or frequency.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose of either Investigational or concomitant medication ***without*** any signs or symptoms. Note: Overdose should be recorded in special situation dedicated forms and reported to sponsor or designated vendor within 24 hours.

A clinically significant laboratory assessment (as determined by the Investigator) is considered an AE and must be recorded in patients' source documents and the eCRF.

Disease progression is a worsening of a patient's condition attributable to the disease for which the trial medication is being given. This may be an increase in severity of the disease or an increase in the symptoms of the disease. Disease progression itself and death from disease progression should not be recorded as an AE.

However, new or increasing symptoms not related to disease progression should be reported as AEs.AE.

9.2 Recording Adverse Events

All AEs must be reported from the time of ICF signature through the point of tinostamustine discontinuation. Only AEs ongoing at time of Tinostamustine Discontinuation Visit are required to be followed to resolution or stabilization of event and then final resolution date is recorded in the AE eCRF.

During Follow-up, any new SAE commencing within 30 days of Tinostamustine Discontinuation should be recorded and followed to resolution.

Whenever possible, a diagnosis should be given when signs and symptoms are due to common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as 'upper respiratory infection'). AE reporting and severity grading will be assessed using the NCI CTCAE, version 4.03 (June 2010), with the exception that in Phase 2, QTc prolongations will be assessed for severity using CTCAE version 5.0. For those events without assigned CTCAE grades, the recommendation on page 1 of the CTCAE that converts mild, moderate, and severe into CTCAE grades should be used. A copy of the NCI CTCAE is available online at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **Seriousness**

For definition of seriousness criteria refer to Section 9.3. All seriousness criteria that apply have to be recorded.

- **Action Taken with tinostamustine**

The action taken with tinostamustine as a result of the AE has to be documented. In the situation that the AE leads to permanent discontinuation of tinostamustine, this meets the definition of an AE leading to Subject's withdrawal from the study.

- **Treatment for the AE**

Any treatment for an AE, whether pharmacological or other (e.g. surgical) treatment, has to be recorded in the eCRF.

- **Outcome**

The outcome recorded should be reflective of the outcome at the time of reporting the AE. The following categories should be used:

  - **Not recovered/Not Resolved**
    - Indicates that the event is ongoing and there has been no recovery.
  - **Recovering/Resolving**
    - Indicates that the event is in the process of recovery but has not yet fully resolved.
  - **Recovered/Resolved**
    - Indicates that the event has fully resolved.
  - **Recovered/Resolved with sequelae**
    - Indicates that there is a residual, possibly permanent consequence of the event (e.g. residual hemiparesis subsequent to stroke).
  - **Fatal**
    - Indicates that the Subject died due to the event. The outcome "fatal" applies only to the event(s) that were the cause(s) of death. For other adverse events that were ongoing at the time of death, the outcome must be recorded as "not recovered" and not "fatal".
  - **Unknown**

Indicates that the outcome of the AE cannot be determined despite the best efforts of the Investigator. This may be due to the Subject being 'Lost to Follow-up' and therefore the Safety Follow-Up visit could not be performed.

- **Causal Relationship of AE**

The causal relationship of all AEs to tinostamustine treatment will be determined by the Investigator according to best medical judgment, as follows:

- Definitely related: This category applies when, after careful medical consideration, there is almost no consideration of other causation.
- Probably related: There is a clinically plausible time sequence between onset of the AE and trial treatment administration. The AE is unlikely to be caused by a concurrent and/or underlying illness, other drugs, or procedures. If applicable, the AE follows a clinically consistent resolution pattern upon withdrawal of tinostamustine.
- Possibly related: There is a clinically plausible time sequence between onset of the AE and trial treatment administration, but the AE could also have been caused by the concurrent/underlying illness, other drugs, or procedures. Information regarding tinostamustine withdrawal may be lacking or unclear. "Possible" should be used when trial treatment administration is one of several biologically plausible causes of the AE.
- Unlikely related: The AE is most likely due to a non-trial-treatment-related cause. However, association with the trial treatment cannot be completely ruled out.
- Unrelated: Another cause of the AE is most plausible, and a clinically plausible temporal sequence is inconsistent with the onset of the AE and trial treatment administration and/or a causal relationship is considered biologically implausible.

For the causality assessment of QTc prolongations, see Section 9.4.

For the purpose of regulatory reporting requirements, causal relationship criteria given as definite, probable, and possible will be considered treatment-related, while unlikely and unrelated will be considered not treatment-related.

- **Follow up of AE**

Adverse events should be followed up to determine the outcome. The cut off for information collection in the eCRF for AEs and SAEs including any follow up lab information is according to Section 9.2. Any AE that is still ongoing at this visit will have an outcome of 'Recovering/Resolving' or 'Not Recovered/Not Resolved' in the eCRF. After that all information still needs to be collected in the source and for SAEs the information needs to be forwarded to the Sponsor.

- All efforts to collect follow-up information must be documented in the Subject's source data as soon as it is received.
- All AEs must be followed up by the Investigator until:
  - the AE is resolved or resolved with sequelae and all other queries related to the AE have been clarified, or
  - the end of the period of observation (= last study visit), or
  - the Investigator considers it medically justifiable to stop further follow-up

- If the Subject had an AE with fatal outcome, an autopsy report should be provided if possible.
- If SAEs are ongoing at the time of the Subject's last study visit, an additional safety follow-up visit should be scheduled for those Subjects. This visit will be documented in the source notes and not in the eCRF.
    - The Investigator should set the interval to the additional safety follow-up visit according to his/ her medical judgement. If the EDC system is closed, information from this visit should be forwarded to the Sponsor using the paper SAE form.
- The Investigator should respond to any queries raised by the Sponsor in relation to adverse events, including provision of supporting documentation within the requested timeline.
    - In case of fatal or life-threatening SAEs the Sponsor may request urgent clarification within one business day.

Subjects who were treated with IMP but did not complete the study as per protocol, should receive all the examinations and investigations scheduled for the last study visit. The Investigator should make all efforts to contact Subjects lost to follow-up and document the attempts in the Subject's source data.

9.3 Serious Adverse Events

A SAE is any AE that is considered 'serious' if, in the view of either the Investigator or Sponsor, it results in any of the following:

- Is fatal;
- Is life-threatening (defined as an immediate risk of death from the event as it occurred);
- Requires in-patient hospitalization or prolongation of existing hospitalization (Exception: Hospitalization for elective treatment of a pre-existing condition that did not worsen during the trial and is not considered an adverse event. Note: Complications that occur during hospitalization are adverse events and if a complication prolongs hospitalization, then the event is serious);
- Results in persistent or significant disability/incapacity, or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly/birth defect;
- Important medical events may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the SAE criteria listed in this definition.

Examples of important medical events which may meet the definition of a SAE include: intensive treatment in the emergency room or at home for allergic bronchospasm, certain abnormalities (e.g., blood dyscrasias), convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Events exempt from immediate reporting as SAEs.

Hospitalization for pre-existing conditions e.g. elective procedures planned prior to study entry, which has not worsened do not require SAE reporting. All events related to disease progression, including

events resulting in death, are not considered SAEs. They need to be nevertheless clearly documented as events due to disease progression in the eCRF.

9.4 Events of Special Interest

Based on data obtained across the development program of tinostamustine, the Sponsor has identified QTc prolongations as events of special interest for which the following reporting requirements apply based on local ECGs:

1) All QTc prolongations Grade 2 need to be reported as AEs by entering them in the AE section of the eCRF
2) All QTc prolongations Grade 3 (per the most recent CTCAE 5.0 criteria) are to be considered clinically significant and need to be reported as SAEs if they fulfill the following criteria:

   QTcF >500 ms or QTcF increase from baseline >60 ms

Note that either 1 or >1 occurrence within 1 treatment cycle of 28 days will be regarded as 1 single event. Occurrences in more than 1 treatment cycle will be regarded as separate events in 1 patient.

For events meeting criterion 2, an SAE report form needs to be submitted as for all other SAEs.

Based on available PK data, a causal relationship with tinostamustine has to be assumed, if the QTc prolongation occurs within 6 hours from the start of tinostamustine infusion. Therefore, all SAEs identified as per point 2 above will be considered Serious Adverse Drug Reactions (SADR).

9.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions qualify as SUSARs if the following 3 conditions are met:

1. the event must be serious;
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Investigator’s Brochure for an unauthorized medicinal product:
   - For this trial, the most current IB version contains the Reference Safety Information for the expectedness assessment

9.6 Reporting of AEs, SAEs, Serious and Unexpected Adverse Experiences

9.6.1 Reporting AEs and SAEs to the Sponsor

All AEs must be reported in the eCRF from the time of ICF signature to the point of tinostamustine discontinuation. Only AEs ongoing at time of Tinostamustine Discontinuation Visit are required to be followed to resolution or stabilization of event and then final resolution date is recorded in the AE eCRF. During Follow-up, any new SAE commencing within 30 days of tinostamustine discontinuation should be recorded and followed to resolution. If the Investigator becomes aware of safety information that appears to be drug related, involving a patient who participated in the trial, even after an individual

patient has completed the trial, this should also be reported to the Sponsor or the designated vendor. In addition, all treatment related SAEs should be followed until resolution or stabilization.

All SAEs, regardless of relationship to tinostamustine, must be additionally reported to the Sponsor or the designated vendor within 24 hours of the Investigator becoming aware of the event using the SAE form. Follow-up SAE reports must be submitted by the Investigator as new information becomes available or as requested by the Sponsor or designated vendor. Supportive source documents have also to be provided together with the SAE form.

- All SAEs have to be reported via e-mail or fax by using the Mundipharma **SAE Report Form** and a cover page which are available in the Investigator site file. The SAE reporting contact of the Sponsor is Mundipharma Drug Safety & PV.

Mundipharma Drug Safety and PV	Tel: +44 (0) 1223 424444 (Not 24-hour coverage; for 24-hour details please see the Investigator Site file) Fax: +44 (0)1223 426002 E-Mail: drugsafetycentral@mundipharma-rd.eu

9.6.2 Reporting Suspected Unexpected Serious Adverse Reactions

The responsibility for expedited reporting of SUSARs within 7 days (life-threatening and death cases) or 15 days (all other SUSARs) is with the Sponsor or its delegated vendor.

The Sponsor or designated vendor will report to the regulatory authorities as per national regulations of the countries where the ongoing tinostamustine trials are conducted and will provide the case documentation to the CROs for reporting to the applicable IRBs/IECs.

Investigators will be informed as per national requirements.

9.6.3 Reporting of Grade 4 and Grade 5 AEs

All grade 4 AEs (per definition "life-threatening") and grade 5 ("death"), as per CTCAE, version 4.03, that occur during the trial are to be reported as SAEs, with the exception of Grade 4 laboratory abnormalities, which are to be reported as SAEs only if, in the Investigator's judgement, they are considered immediately life-threatening.

9.6.4 Reporting of Important Medical Events of Special Interest

Important medical events (IME) of a clinically significant severity grade (≥Grade 3) may also qualify as SAEs. To establish consistency across trials with tinostamustine, the IME list published by the European Medicines Agency and regularly updated (current version April 2019) serves as a reference.

9.6.5 Reporting Pregnancy

If a female patient or the female partner of a male patient becomes pregnant during the course of the trial and within 90 days from the last dose administration, the Investigator must report the pregnancy to the Sponsor or its designated vendor, using the **Pregnancy Reporting Form** within **24 hours** of becoming aware of the event. The Investigator must obtain consent to collect pregnancy information

(including the status of the newborn, if applicable). If possible, pregnancy needs to be followed up until its termination (birth, abortion, miscarriage).

If some of the information required for completion of the Pregnancy Reporting Form is unavailable at the time of the initial report, follow-up reports will be completed and submitted within 24 hours of becoming aware of the new information. The Investigator is required to follow the pregnancy through delivery. The outcome of the pregnancy and the status of the newborn (if applicable) will be reported on the Pregnancy Reporting Form within 24 hours of becoming aware.

9.6.6 Reporting to the IRB/IEC

SAEs will be reported to their IRB/IEC by the Investigator according to the IRB/IEC's policy and procedures.

9.6.7 Annual Safety and Progress Reports (DSUR)

In addition to the expedited reporting of SUSARs, the Sponsor will submit, once a year throughout the clinical trial, a safety and progress report in DSUR format to applicable competent authorities. The DSUR or an Executive Summary of the DSUR will be submitted to the IRBs/IECs as applicable per local requirements.

10 STATISTICAL ANALYSES

10.1 Trial Populations

10.1.1 Full Analysis Population

All patients who received at least 1 dose of trial treatment and had at least 1 post-baseline response evaluation will be included in the Full Analysis (FA) Population. Efficacy analyses will be performed on data from all patients in the FA Population.

10.1.2 Safety Population

All patients who received at least 1 dose of trial treatment will be included in the Safety Population. Safety analyses will be performed on data from all patients in the Safety Population.

10.1.3 Pharmacokinetic Population

All enrolled patients in the Safety Population with at least 1 quantifiable pre-dose and 1 quantifiable post-dose PK plasma concentration in Cycle 1 will be included in the PK Population. PK analyses will be performed using the PK population.

10.2 Unit of Analysis

Not applicable.

10.2.1 Sample Size and Power Considerations

A formal sample size determination and power calculation were not performed. Based on experience from previously published similar trials, a total number of 21 (minimum) to 42 (maximum) patients in the dose escalation stage of the trial and 56 to 160 patients (10 or 29 evaluable patients in each of the 5 disease cohorts) in the expansion stage of the trial are considered to be sufficient for meeting the objectives of this trial, following Simon's optimal 2-stage design methodology[13]. Assuming the proportion of treatment successes that do not warrant further investigation (π_0) is 0.10, the proportion of treatment successes that warrant further investigation (π_1) is 0.30, an 80% power and a 5% Type I error rate. The one-sided hypotheses to be tested are:

H_0: $\pi \leq \pi_0$

H_1: $\pi \geq \pi_1$

where π is the actual probability of success.

In stage 1, 10 patients will be treated in each cohort; potential efficacy and the decision to expand into stage 2 or not may be taken prior to the 10th patient completing the study. During the assessment of stage 1, enrollment into the expanded cohort (stage 2) will continue. However, it is anticipated that new patients will enroll infrequently due to the expected low recruitment rate. From stage 1, if there are no successes or only 1 success in the 10 stage 1 patients, the complete cohort will be stopped for lack of efficacy. If there are 2 or more successes in stage 1 an additional 19 patients may be treated for a total of 29 in a cohort. If it becomes clear that there will be 5 or fewer successes in a cohort of 29 patients, then the cohort will be stopped for lack of efficacy.

The Sponsor may suspend or discontinue enrollment to an expansion cohort at any time due to slow patient accrual rates or other reasonable cause.

10.3 Data Analysis

A detailed SAP will be finalized prior to any statistical report and database lock.

In general, summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation, median, minimum, and maximum. Summaries for discrete variables will include frequency counts and percentages. All statistical tests, if any, will be 2-sided with a significance level of 0.10 unless otherwise specified. Additionally, 90% confidence intervals will be reported.

10.3.1 Demographics and Baseline Characteristics

Demographic information will include age, gender, ethnicity and race[11,12] Demographics and baseline characteristics will be summarized descriptively. Height and weight, which will be recorded in conjunction with vital sign determinations performed at the Screening visit, will be reported with the demographic information listed above. Patient demographics: gender, ethnicity, race, and age category will be presented using discrete summary statistics. Age, height, and weight will be presented using continuous summary statistics.

10.3.2 Safety Analysis

For Phase 1, patient safety data were summarized under the dose cohort in which they were enrolled.

For Phase 2, patient safety data will be summarized by disease cohort as well as overall disease cohorts. (i.e., relapsed/refractory SCLC, relapsed/refractory STS, relapsed/refractory TNBC, relapsed/refractory ovarian cancer, relapsed/refractory endometrial cancer).

Additionally, as appropriate, Phase 1 and Phase 2 safety measures will be summarized combining Phase 1 measures obtained under RP2D and schedule with Phase 2, accounting for disease cohort.

The safety analysis will summarize AEs for all treated patients using discrete summaries at the patient- and event-level by system organ class and preferred term. An AE will be defined as occurring on or after the day that treatment is initiated. AEs, AEs leading to death, SAEs, and AEs resulting in trial discontinuation will be summarized similarly. AEs will also be summarized by NCI-CTCAE Grade. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) for purposes of summarization. All AEs occurring during the trial will be included in by-patient data listings and tabulated.

Safety analyses are described in detail in the SAP.

10.3.3 Efficacy Analyses

Efficacy variables of Phase 2 patients will include ORR (i.e. CR or PR of any duration), plus SD of at least 4 months, duration of response, PFS, and OS. CR, PR, SD are defined by RECIST criteria (Section 13.3).

Response rates will be summarized using discrete statistics by disease cohort as well as all disease cohorts combined. Post-treatment RECIST assessments are used to determine best overall response. PFS is defined as the number of days between the date of the first dose of treatment and the first date of disease progression or death. Overall survival is defined as the number days between the date of the first dose of treatment and the date of death. PFS and OS will be estimated using Kaplan-Meier method. The estimated survival probabilities will be presented via Kaplan-Meier curves

and median survival will be reported. The survival analysis will be performed by disease cohort as well as all disease cohorts combined. Handling of censoring will be discussed in full in the SAP.

10.3.4 Pharmacokinetic Analysis

PK analysis will be performed using the PK population. PK parameters at all doses will include C_{max}, T_{max}, half-life, AUC_{0-12}, AUC_{0-t}, clearance, volume of distribution, and elimination rate constant. Other PK parameters may be calculated, as appropriate. The initial calculation of PK parameters will be performed using non-compartmental analysis. Model-based parameter estimation may be performed following examination of the data. Plasma concentrations and PK parameters will be summarized using continuous statistics by dose and infusion time. Figures will be created to display mean and individual patient tinostamustine and its 2 metabolites concentration-time curves in plasma on a linear scale as well as on a semi-log scale. Plasma concentrations will be processed throughout the PK software for PK data generation. The PK parameters were calculated by non-compartmental analysis (NCA), using Phoenix® WinNonlin® (Version 8.1 – Certara – Princeton – USA). Handling of concentrations below limit of quantitation (BLOQ) will be detailed in a separate analysis plan.

For Phase 1, patient data will be summarized under the dose level and schedule they received for the Cycle being summarized.

For Phase 2, patient data will be summarized by disease cohort (if sample size permits) as well as overall disease cohorts.

Additionally, as appropriate, Phase 1 and Phase 2 measures will be summarized combining Phase 1 measures obtained under RP2D and schedule with Phase 2.

Additional details regarding PK analyses are provided in a separate PK SAP.

10.3.5 Deviations from the Statistical Plan

Any deviation(s) from the final SAP in the final analysis will be described and justification given in the final report.

11 TRIAL ADMINISTRATION

11.1 Case Report Forms and Source Documentation

In order to provide the Sponsor/CRO with accurate, complete, and legible data, the following criteria are to be maintained:

- Source documents will be completed according to a source document agreement outlining all the data that is to be collected in the source documents throughout the trial.
- Investigator/institution should maintain adequate and accurate source documents that include all pertinent observations on the trial patients. Source data should be attributable, legible, contemporaneous, original, accurate and complete. Changes to the source data should be traceable, should not obscure the original entry and should be explained if necessary

Electronic data capture (EDC)/eCRF entries should be made as close to the visit of the subject as possible. Data reported on the eCRF should be completed accurately and in a timely manner according to the eCRF guidelines and add ICH E6 R2 4.9.2 and 4.9.3.

11.2 Good Clinical Practice Statement

This trial is to be performed in full compliance with the protocol, the Declaration of Helsinki, ICH, and all applicable local Good Clinical Practices (GCP) and regulations. All required trial documentation will be archived as required by competent authorities.

11.3 Investigator Documentation

The Investigator will provide the Sponsor with a fully executed FDA form 1572 (or applicable alternative Investigator statements) including the Investigator’s curriculum vitae.

11.4 Record Retention

The circumstances of completion or termination of the trial notwithstanding, the Investigator has the responsibility to retain all trial documents, including but not limited to the protocol, Investigator's Brochure/Summary of Product Characteristics (SmPC), regulatory agency registration documents, ICFs, and IEC correspondence, according to ICH E6 (R2) requirements.

The site should plan on retaining trial documents for approximately 15 years after completion of the trial. This will include copies of the completed eCRF/EDC. The investigator should have control of and continuous access to the eCRF data.

It is requested that at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contact the Sponsor, allowing the Sponsor the option of permanently retaining the trial records. Records retained will be stored independently of the Sponsor, and the Sponsor will not be permitted direct access to this data. The measures implemented for the archiving in a separate location from the sponsor (i.e. an archiving depot) and the access of the site to these records, will be provided to the site if necessary.

11.5 Protocol Deviations and Amendment

The Investigator is not permitted to alter or deviate from the protocol. All deviations should be reported by the Investigator to their IRB/IEC. An immediate and unapproved deviation is permitted if immediate health care concerns mandate it.

All protocol revisions (Amendments) must originate with and be documented by the Sponsor. In the US, the Investigator must submit all amendments to his/her IRB/IEC for review and approval prior to implementation; documentation of approval signed by the chairperson or designee must be sent to the Sponsor.

11.6 Institutional Review Board and Independent Ethics Committee

Federal regulations and ICH require that approval be obtained from an IRB/IEC prior to participation of patients in research trials. Approval by the Competent Authority, if applicable, or as required by local laws and regulations, is also required in Europe. Prior to the trial onset, the protocol, any protocol amendments, ICFs/assent forms, advertisements to be used for patient recruitment, and any other written information regarding this trial to be provided to a patient or patient's legal guardian, must be approved by the IRB/IEC.

All IRB/IEC approvals must be dated and signed by the IRB/IEC Chairperson or designee and must identify the IRB/IEC by name and address, the clinical protocol by title and/or protocol number, and the date approval or favorable opinion was granted for the clinical research.

No drug will be released to the site to dose a patient until written IRB/IEC authorization has been received by the Sponsor or designee.

The Investigator is responsible for obtaining continuing review of the clinical research at least annually or more often if specified by the IRB/IEC. The Investigator must supply the Sponsor or designee with written documentation of the approval of the continued clinical research.

The Investigator, sponsor, or its designee as applicable, will make all attempts to ensure that the IRB/IEC is constituted and operates in accordance with Federal and ICH GCP and any local regulations.

In the case of early termination/temporary halt of the trial, the Investigator should notify the IRB/IEC and Competent Authority (CA) within 15 days and a detailed written explanation of the reasons for the termination/halt should be given. If the IEC decides to suspend or terminate the trial, the Investigator will immediately send the notice of trial suspension or termination by the IRB/IEC to the CRO.

At the end of the trial, the Sponsor should notify the IRB/IEC and CA within 90 days. The end of the trial will be the date of the last scheduled trial visit for the last Subject in the trial. The Sponsor will always also provide the IRB/IEC/CA with a summary of the trial's outcome.

11.7 Sponsor Monitoring and Auditing

After satisfactory receipt of the Clinical Trial Agreement and all other necessary regulatory paperwork, the Sponsor's monitor will arrange that all trial material be delivered to the trial site at a mutually convenient time. An initiation visit by the Sponsor representative and its monitoring personnel will be made. At this meeting, all personnel expected to be involved in the conduct of the trial will undergo

an orientation to include review of trial protocol, instruction for eCRF completion and overall responsibilities, including those for drug accountability and trial file maintenance.

Throughout the course of the trial, the Sponsor's representative monitor will make frequent contact with the Investigator. This will include telephone and/or on-site visits. During these visits, eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data verification process, it is expected that source documents (e.g., hospital records, office records) will be made available for review by the monitor. The monitor also will perform drug accountability checks and may periodically request review of the Investigator's trial file to ensure completeness of documentation in all respects of trial conduct.

Upon trial completion, the monitor will arrange for a final review of the site trial files, after which the file should be secured by storage for the appropriate period as specified in Section 11.4.

Audits will be conducted on a frequency which is based on risk and proportionate to the complexity of the trial. Additional audits may be performed if there is cause for concern or when requested by Sponsor, CRO, or competent authority. Regular audits will usually be performed with advance notice. Audits may be performed without notice. Authority inspections may occur at any time as deemed appropriate by the responsible authority in the country.

Audits and authority inspections may be performed without notice, especially where the Sponsor or competent authority deems necessary to investigate patient safety, welfare, scientific integrity, compliance and/or fraud (a for-cause audit). The Investigator is required to support audit or authority inspections, to be available to the auditors/inspectors upon request and to permit the auditor/inspector direct access to source data/documents.

11.8 General Informed Consent and Sub-trial Informed Consent for Genetic Samples

The Investigator will explain the nature of the trial as described in the general ICF and will inform the patient that participation is voluntary and that they can withdraw at any time and that withdrawal consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

Information on the purpose of genetic research in the gene-expression sub-trial is provided, either in the main ICF or a separate ICF to allow the patient to decide whether he or she want to participate in this part of the trial. Participation in this genetic research is voluntary.

The applicable ICFs must be approved by the IRB/IEC before use in the clinical trial.

The subject will be asked to sign and date the ICF prior to any trial-specific procedures being performed. The subject should understand the ICF before signing and dating the ICF. The Investigator or person obtaining consent must also sign and date the form. Each subject will be given a copy of the signed informed consent and written information. No subject can enter the trial before his/her informed written consent, and in the USA the Health Insurance Portability and Accountability Act (HIPAA) authorization] has been obtained. Each patient's signed ICF, including additional ICFs signed (e.g. for re-consent, and the pharmacogenomic sub-set) must be kept on file by the Investigator for possible inspection by regulatory authorities and/or the Sponsor personnel.

Each patient's signed informed consent form must be kept on file by the Investigator for possible inspection by regulatory authorities and/or the Sponsor personnel.

11.9 Confidentiality

The Investigator and his staff shall maintain the confidentiality of all patient records. Patient data will be made available to CRAs and auditors commissioned by the Sponsor, and to FDA and other competent authorities during inspections.

Data that is transmitted by the Investigator to the Sponsor, competent authority, or IRB/IEC will not be directly traceable to the patient. In the event that a publication of this research incorporates a patient's medical data, that data will not identify the patient. The subject's name will not appear on documents transmitted to the Sponsor in order to maintain confidentiality. Additional anonymization/pseudonymization laws as applicable by country will also be adhered to.

Processing of data and/or samples will be carried out in accordance with federal and local regulations. This applies to all trial data in whatever format it is collected and recorded.

11.10 Financial Disclosure

The Investigator and sub-investigators, as noted on the Form FDA 1572 (or applicable alternative Investigator statement), shall provide the Sponsor with accurate financial disclosure information as required under 21 Code of Federal Regulations (CFR) 54. The Investigator shall promptly update this information if any relevant changes occur during the trial and for 1 year following the completion of the trial.

11.11 Reporting and Publication Policy

The Sponsor will determine the identity of the Co-ordinating Investigator for the trial who will review and sign off the Clinical Trial Report. This decision will be based on involvement in the trial including, but not limited to, trial design, Subject recruitment and interpretation of trial data.

Clinical trials will be registered in public databases and summary results released / disseminated via publicly available clinical trials databases according to the Sponsor's standard operating procedures (SOPs) and local requirements. As a general rule, both Phase 1 Healthy Volunteer studies and trials using a medicinal product in the normal course of medical practice (for example Non-Interventional trials and Post Marketing Surveillance trials), are excluded from the above public registration and reporting requirements. If such trials and trials do require public registration and/or reporting, this will be undertaken according to local requirements.

The Sponsor registers clinical trials and posts the summary results as required by local and federal regulations.

Following the end of the clinical trial, the summary results should be made publicly available according to accepted timelines and requirements, usually within 12 months of trial completion. For multi-site trials, it is mandatory that the first publication be based on data obtained from all analyzed Subjects; therefore, Investigators participating in multi-site trials must not present data gathered individually or by a subgroup of sites prior to the full, initial publication, unless this has been agreed to by all other Investigators and the Sponsor. Publication of clinical trial results may include the presentation of such work at national and international congresses, symposia, professional meetings, peer-reviewed journals, and via other appropriate channels. Named authors and contributors to such publications shall be determined by the Sponsor in accordance with both the Company Publication Policy (which can be found at: http://www.mundipharma-rd.eu/research-areas/publications.html) and the generally accepted criteria for authorship as outlined by the ICMJE authorship guidelines. The data associated

with any publication will be and shall remain the sole property of the Sponsor; the copyright of the document may be transferred to the scientific peer-reviewed journal prior to and as part of the publication process, as appropriate.

Subject to the paragraph above, the site may publish or present the results of the clinical trial subject to the protection of the Sponsor or its nominee(s) intellectual property rights, know- how, and its proprietary information. The Sponsor must be furnished with a copy of any proposed publication or presentation at least 60 days prior to submission for review and comment. Upon notice by the Sponsor, however, that the Sponsor intends to secure its intellectual property rights (for example, file a patent application relating to the trial) or that Sponsor requires for its know-how or proprietary information to be removed prior to such publication, such publication may be delayed for a further 6 months or until its intellectual property rights have been secured, whichever is the later. The site further agrees that Sponsor's reasonable comments in relation to the proposed publication will be incorporated into the publication.

11.12 Insurance

The Sponsor shall have clinical trial insurance in accordance with applicable national regulations. This insurance provides cover for damage to research participants through injury or death caused by trial participation and is independent of investigational drug causality.

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13 APPENDICES

13.1 Appendix A: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale[10]

ECOG Performance Status	
Grade	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

13.2 Appendix B: NYHA Functional Classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs, etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20 to 100 meters). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

13.3 Appendix C: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

QUICK REFERENCE

Eligibility

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

— **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

— **Measurable lesions** - lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray.

Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At Baseline and follow-up, only the short axis will be measured and followed.

— **Non-measurable lesions** - all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

- For special considerations regarding lesion measurability for bone lesions, cystic lesions and lesions with prior local treatment, consult the RECIST 1.1 guidelines in the Study Reference Manual.
- All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before beginning of treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, either a CT scan or documentation by color photography, including a ruler to estimate the size of the lesion, is to be done.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm

contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the trial is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

— **Target Lesions** - all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.

  - Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
  - A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

— **Non-target lesions** - all other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria:

Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm).

Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions from the smallest sum of the LD recorded since the treatment started; the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of ≥1 new lesion is also considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

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

* Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or trial chair).

Evaluation of best objective response

- The best objective response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target Lesions	Non-Target Lesions	New Lesions	Objective Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD

PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such trials that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the trial protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the trial protocol

Duration of objective response

- The duration of objective response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specifies the minimal time interval required

between 2 measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Definition of CT tumor response by RECIST 1.1 criteria:

The following table outlines the response categories by RECIST 1.1 criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
Complete Response (sum of diameters=0 mm)	Complete response	No	Complete Response
Complete Response	Non-complete response, non-progressive disease	No	Partial Response
Complete Response	Not evaluated	No	
Partial Response (decrease in sum of target lesions by ≥30%)	Non-progressive disease OR Not evaluated	No	
Stable Disease	Non-progressive disease OR Not evaluated	No	Stable Disease
Not all evaluated	Non-progressive disease	No	Not Evaluable
Progressive Disease (increase in sum of target lesions by ≥20% with an absolute increase in summed diameters by 5mm)	Any	Yes or No	Progressive Disease
Any	Progressive Disease	Yes or No	
Any	Any	Yes	

E.A. Eisenhauer, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) European Journal of Cancer 45 (2009) 228–247 doi:10.1016/j.ejca.2008.10.026.

13.4 Appendix D:ASCO and CAP Guidelines on HER2 Testing in Breast Cancer

To determine HER2-negativity, IHC or in situ hybridization can be used. Below are the CAP guidelines as a reference:

HER2 Testing by Immunohistochemistry (IHC):

Negative (Score 0): No staining observed or Incomplete, faint/barely perceptible membrane staining in ≤10% of invasive tumor cells

Negative (Score 1+): Incomplete, faint/barely perceptible membrane staining in >10% of invasive tumor cells

HER2 Testing by In Situ Hybridization:

Reporting Results of HER2 Testing by In Situ Hybridization (single-probe assay):

Negative (not amplified): Average HER2 copy number <4.0 signals/cell

Reporting Results of HER2 Testing by In Situ Hybridization (dual-probe assay):

Negative (not amplified): HER2/CEP17 ratio <2.0 AND average HER2 copy number <4.0 signals/cell