Mundipharma Research limited

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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Statistical Analysis Plan

Version 2.0

Final

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CROMSOURCE

Signature Page

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Version History

Version	Date	Reason for Change
1.0	21-AUG-2018	This is the first version, based on the CROMSOURCE SAP template. This version is restricted to the analysis of the phase 1 data for the RP2D Decision Report. However, the Table of Contents and its underlying structure already reflect the extent of the full analysis of the phase 1 and phase 2 parts of the study. Any part that is not applicable for the analysis for the RP2D report is indicated as such with “NA for RP2D”.
2.0	02-MAR-2021	To cover the complete final analysis. To account for changes to the protocol since the first version of SAP.

Table of Contents

1. SOPs to be followed

The statistical analysis is carried out according to the following CROMSOURCE SOPs:

SOP number	SOP title
SOP-ST-03	Statistical Analysis Plan
SOP-ST-04	SAS Programming and Validation
SOP-ST-05	Data Review Meeting
SOP-ST-08	Trial Statistics File

2. Abbreviations

Abbreviation	Explanation
ADaM	Analysis Data Model
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSA	Body surface area
BUN	Blood urea nitrogen
C	Cycle
CDISC	Clinical Data Interchange Standards Consortium
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DLT	Dose-limiting toxicity
DME	Dose modifying event
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
GGT	Gamma-glutamyl transaminase
Gy	Geigy
HDACi	Histone deacetylase inhibitor
HLGT	Higher Level Group Term
HLT	Higher Level Term
hr	Hour

Abbreviation	Explanation
HR	Heart Rate
ID	Identification
i.v.	Intravenous; Intravenously
IND	Investigational New Drug
LD	Lesion Diameter
LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
LLT	Lower Level Term
LOCF	Last Observation Carried Forward
MAD	Maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MS	Microsoft
MTD	Maximum tolerated dose
NA	Not applicable
ORR	Objective response rate
PD	Progressive Disease
PET/CT	Positron emission tomography/computed tomography
PFS	Progression free survival
PK	Pharmacokinetic
PR	Partial response, pulse rate, or the period (interval) from the onset of the P wave until the start of the QRS complex in the heart's electrical cycle
PT	Preferred Term
QC	Quality Control
QRS complex	Graphical deflections on an ECG that correspond to ventricular depolarization
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
QTcB	Corrected QT interval (Bazett)
QTcF	Corrected QT interval (Fridericia)
RBC	Red Blood Cells

Abbreviation	Explanation
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase 2 dose
RR	R wave-to-R wave, inversely related to heart rate
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable disease or standard deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Safety review committee
TEAE	Treatment-emergent adverse event
TLF	Tables, Listings and Figures
TOT	Total Set
ULN	Upper limit of normal
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary
WHO-ATC	World Health Organization Anatomical Therapeutic Chemical

3. Protocol

This S101-1002 study is conducted under the sponsorship of Mundipharma Research limited. The clinical monitoring, data management, statistical analysis and medical writing are performed by CROMSOURCE under contract and in collaboration with Mundipharma Research limited.

The final Statistical Analysis Plan (SAP) provides a detailed description of the statistical methods outlined in the protocol version 7.1, dated 27 September 2020. Pharmacokinetic and pharmaco-dynamic/genetic analysis are handled separately by other parties than Cromsource and so are not subject of the SAP. Data generated by the sub-study (protocol version 6.2) are analysed together with the Phase 2 data but as a separate cohort.

Text that has been copied from the protocol is formatted in italics to indicate that it is identical to the protocol, which should ease the review and avoid unnecessary alterations to text approved in the protocol.

All TLFs (Tables, Listings and Figures) of the interim analysis for the RP2D Decision Report as well as of the final analysis for the Clinical Study Report, with the exception of pharmaco-kinetic and pharmacodynamics/genetics evaluations, are produced by CROMSOURCE.

3.1 Study Objectives

Phase 1 primary objective:

To determine the safety, tolerability, 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 intravenously (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 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.*

3.2 Study 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

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 and schedules are defined as*:*

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*

In the 3+3 design, if one of the 3 patients has a dose-limiting toxicity (DLT), 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. If 2 or more DLTs occur 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 are treated at a dose level with less than 2 DLTs.

Phase 2

In Phase 2 *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*

Each cohort will recruit 10 patients (stage 1) expanding to a possible 29 (stage 2) under a Simon 2-stage design, resulting in a total number of patients treated at 80 mg/m2 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.

Treatment may continue until progression or intolerable toxicity, up to a maximum of 12 cycles.

3.3 Study Schedule

The Schedule of Events according to protocol 7.1 is presented in the below table.

Procedure	***Screening 28 days from Baseline (First Day Investigational Medicinal Product Administration); Scans 28 days from Baseline[14]***	***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		

Procedure	Screening 28 days from Baseline (First Day Investigational Medicinal Product Administration); Scans 28 days from Baseline[14]	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]		
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							
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

Procedure	Screening 28 days from Baseline (First Day Investigational Medicinal Product Administration); Scans 28 days from Baseline[14]	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]		
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 is used for Investigational Medicinal Product calculations of BSA. BSA is 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 is 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 the infusion on C1D1 and 15 min prior to the start of 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 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.

[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: 0.5 hours prior to dose administration, and at 15, 30 and 45 minutes and 1 hour, 75 and 90 minutes, and 2, 3, 6 hours, 24 hours from the start of 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 minutes (-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 protocol 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 protocol 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.*
[15] *Abbreviated physical examination is directed by disease site and symptoms.*

3.4 Efficacy and Safety Variables

For phase 1, main safety variables are the Dose Limiting Toxicity (DLT) in cycle 1 and other clinically significant toxicities that occur after cycle 1 (dose modifying event (DME)).

The main efficacy variables (for phase 2) are related to the tumor assessment. *Radiologic response assessment by computed tomography (CT) scans 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.*

Note that the definitions of these variables are presented in section 7 of this SAP.

3.5 Interim Analyses

An interim analysis is planned for the RP2D Decision Report at the end of phase 1. Another interim report is planned for each disease cohort once a decision on success or failure (Clinical Benefit Response) can be determined for all of the first 10 patients of the first stage of the Simon-Two-Stage design. Further details are provided in section 9 of this SAP.

3.6 Changes in Conduct of Study/Planned Analysis compared to Protocol

Population Definition

According to the protocol *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.*

In view that the first post-baseline Tumor Response evaluation is planned for only around 8 weeks after treatment start and to better follow the ITT principle it was decided to define the Full Analysis Set as all patients who received at least 1 dose of trial treatment.

Duration of SD

According to the protocol *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.* The protocol further says *"Radiologic response assessment by computed tomography (CT) or magnetic resonance imaging (MRI) will be performed at baseline and every 2 cycles"* (with a cycle having 28 days) and *"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".*

From this we conclude that the intention is to have two follow-up response assessments to confirm SD. In the schedule of *every 8 weeks (± 2 weeks)* the earliest this can be achieved is after 12 weeks. It was therefore decided that a Clinical Benefit Response is given, if SD with a duration of at least 12 weeks (84 days) is observed.

4. General Definitions

4.1 Report Language

The TLFs as output of the analyses are prepared in English.

4.2 Analysis Software

The statistical analysis is performed using the SAS® statistical software package (Statistical Analysis System, Version 9.3 or later).

5. Data Preparation

5.1 Data Handling and Medical Coding

For data quality control and medical coding please refer to the Data Management Plan, including the Data Validation Plan in its most recent version.

The following coding dictionaries are used in the analysis:

MedDRA version 20.0 for Adverse Events, Medical/Surgical History, Cancer History and Concomitant Procedures. This comprises the datasets: 1) AECODE; 2) MHCODE; 3) CPCODE; 4) CH01; 5) CH02; 6) CT02; and 7) CT03.

The verbatim event terms are coded to a Lower Level Term (LLT), Preferred Term (PT), High Level Term (HLT), High Level Group Term (HLGT) and a System Organ Class (SOC). Only PT and SOC are used in the analysis.

WHO-DD version of March, 2017 for Prior and Concomitant Therapies. This comprises the datasets: 1) CT01; and 2) WHODRUG.

The Investigator Terms (Generic Medication Name, and Indication) are coded to a WHO-ATC Drug class, a WHO-ATC Drug number, a WHO Drug Name (Preferred Term) and Anatomic Therapeutic Chemical (ATC) level classification to all levels from 1 to 4.

5.2 CDISC

All output as defined in the SAP is generated based on CDISC ADaM datasets following ADaM implementation guide 1.0, as per contract with Mundipharma Research limited. SDTM programming follows SDTM version 1.4 together with SDTM implementation guide 3.2.

Specifications for the ADaM (and SDTM) datasets are described in a separate document.

5.3 SAS-Programming Quality Level

The standard quality level of programming deliverables is applied as per contract.

All statistical output will receive a tailored Quality Control (QC) approach by:

Full independently double programmed reproduction (QC) of CDISC:

- SDTM datasets
- ADaM datasets

Full independently double programmed reproduction (QC) of results of:

- Primary endpoint analysis and its underlying analysis dataset(s) and table(s)
- Analysis population definition and merging

Listings are not double programmed.

All other inferential analyses, tables and accompanying derived analysis datasets (i.e. disposition, demographics, baseline characteristics, secondary endpoints, adverse events) are given a reduced QC involving independent reproduction (i.e. double programming or manual cross checking a subset of patients) of approximately 10% of the summary results.

All tables and listings undergo comparison with specification (i.e. SAP and templates), cross checking with other tables and listings, a sensibility review and SAS-log review.

6. Analysis Populations and Subgroups

6.1 Analysis Populations

Total Set

The Total Set (TOT) consists of all patients who provided informed consent as documented by the "Date of Written Informed Consent Signature" on the 'Informed Consent' eCRF page.

Safety Analysis Set (SAF)

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

On the 'Study Drug Administration' eCRF page, it is recorded whether the patient received tinostamustine (EDO-S101) treatment at any visit date. If so, the patient is included in the SAF.

Full Analysis Set (FAS)

According to the protocol *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 Set (FAS). *Efficacy analyses will be performed on data from all patients in the* FAS.

In view that the first post-baseline Tumor Response evaluation is planned for only around 8 weeks after treatment start and to better follow the ITT principle it was decided to define the Full Analysis Set as all patients who received at least 1 dose of trial treatment.

6.2 Treatment Misallocation

Not applicable as treatment is not randomised.

6.3 Subgroup Definitions

No subgroup analysis is performed.

7. Definition of Time Points and Analysis Variables

7.1 Definition of Time Points

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.

For patients who discontinue trial treatment for reasons other than Progressive Disease (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.

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).

The below table shows how the Visits (per Cycle) are labelled in all TLF outputs. *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.* Note that Study Days 2 and 16 apply only to cycle 1. *If a patient misses a scheduled visit to the trial site, the patient will continue on protocol and attend the next scheduled visit.* Visits are analysed as labelled in the eCRF, no window correction is performed.

	Scheduled Study Day	Scheduled Visit Label	Visit Number
	-28	Screening	0
Cycle Number	Scheduled Study Day within Cycle	Scheduled Visit Label	Visit Number
1	1	Cycle 1 Day 1	1.1
	2	Cycle 1 Day 2	1.2
	15	Cycle 1 Day 15	1.5
	16	Cycle 1 Day 16	1.6
	22	Cycle 1 Day 22	1.7
2 - ≤12	1	Cycle X Day 1	X.1
	15	Cycle X Day 15	X.5
	22	Cycle X Day 22	X.7
	Scheduled day after trial treatment ended	Scheduled Visit Label	Visit Number
	Day 28 of Last Cycle or day of withdrawal	Study Discontinuation	50
	Day 28 of Last Cycle or day of withdrawal	Study Treatment Termination	55
	Follow-up	Scheduled Visit Label	Visit Number
	Every 2 months after end of treatment, every 3-4 months after PD or subsequent cancer therapy	Survival Follow-up, RECIST Follow-up	60.y (y=01, 02, 03...)

Unscheduled visits are associated with a cycle and day according to their date and receive the same visit number extended by an additional decimal in the order of the visits. E.g. the first unscheduled visit on or after cycle 2 day15 receives visit number 2.51, the second unscheduled visit receives 2.52 etc. Event type data like AEs, concomitant medication, RECIST assessments etc. are not associated with a visit number.

All assessments except event type data are labelled according to the nominal Visit identifier on the eCRF page, irrespective of meeting the time windows as specified in the study plan.

Study Day

For event type data, including the major safety variables DLT and DME, the Study Day of an event is calculated relative to the First Study Treatment Administration as documented on the Study Drug Administration eCRF at Cycle 1, Day 1. The Study Day of events occurring before the First Study Treatment Administration is calculated as:

Study Day = (Date of event - Date of First Study Treatment Administration).

For events/assessments occurring on or after First Study Treatment Administration, Study Day is calculated as:

Study Day = (Date of event - Date of First Study Treatment Administration) + 1.

Baseline

The Baseline value is defined as the last recording before start of the first dosing. This is at the screening or at the Cycle 1 Day 1 visit (if recording is done before first treatment application) as labelled above.

Last available visit date

The Last available visit date is defined as the last of all visit dates (visits during treatment cycles, unscheduled visit, study discontinuation visit, FU-Visits (for Survival (where status is “Alive”) or for RECIST)) or the last of all Tumor Response Assessment dates or the date of completion/discontinuation as recorded on the Study Termination eCRF page - whichever is latest.

Date of death

The date of death is as documented on the Study Termination eCRF page or a Survival Follow-up eCRF page.

Day of death

The study day of death is calculated as

Day of Death = (Date of Death - Date of First Study Treatment Administration) + 1

Date of Progression

The date of Progression is defined as the earliest date of tumor response assessment with an Investigator’s Overall Response of Progressive Disease.

Date of last available RECIST assessment

The Date of last available RECIST assessment is the latest date of a post-baseline RECIST Tumor response assessment that has the Investigator's Overall Response recorded.

7.2 Event Dates

Medical events are defined as medical history, cancer history, concomitant medication, concomitant procedures, cancer therapies and adverse events.

7.2.1 Event Days

All types of events have a Start/Onset Day calculated and, if not 'Ongoing', have a Stop/Resolution Day calculated equivalent to Study Day as defined in 7.1.

7.2.2 Missing Dates and/or Times

Missing and/or incomplete dates/times for events are imputed for calculating Start Day and Stop Day only. Dates are listed as missing/incomplete [with "-" replacing missing information] but the Start/Stop Day/Time are listed between square brackets to denote it is calculated based on missing data (i.e. [-28], [1], [Ongoing]).

Missing and/or incomplete dates/times are imputed in a manner that assumes the worst-case scenario (i.e., Start as close as possible to the First Study Treatment Administration and stopped such that it is assumed to have lasted for the longest possible duration, taking into account that the Start date/time should not be after the Stop date/time).

Technically, this is done as follows for Stop Day/Time:

- For a completely missing stop year (regardless of minute, hour, day or month response) the event is assumed to be ongoing.
- For a missing stop hour (and the event is not 'Ongoing'):
  - it is assumed to have ended on hour 23 (11pm) of that day
- For a missing stop minute (and the event is not 'Ongoing'):
  - it is assumed to have ended 59 minutes past the hour
- For a missing stop day (and the event is not 'Ongoing'):
  - it is assumed to have ended on the last day of the month, if the month is given
  - it is assumed to have ended on the 31st of December of that year, if the month is also missing

Technically, this is done as follows for Start Day/Time:

- For a completely missing Start date (day, month and year regardless of the minute and hour recorded)
  - the Start Day of the event is "[Pre-Treat]" if the stop date or partial stop date concludes the event stopped before First Study Treatment Administration (i.e. assumed to be prior or pre-treatment as is applicable).
  - in all other instance (i.e. inconclusive stop date or Ongoing event) the Start Day of the event is assumed to be the same date and time as First Study Treatment Administration (i.e. assumed to be concomitant or treatment emergent as applicable.)
- For a missing start hour:
  - it is assumed to have started on hour 00 (midnight) of that day.
  - or at the time (hour and minute) of First Study Treatment Administration if the start date (day, month and year) is the same as the First Study Treatment Administration date.
- For a missing start minute:
  - it is assumed to have started on minute 00 of that hour.
  - or at the time (hour and minute) of First Study Treatment Administration if the start date (day, month and year) is the same as the First Study Treatment Administration date.
- For a missing Start day but given month:

- it is assumed to have started on the first day of the month.
- or at the date of First Study Treatment Administration if the start month and the year is the same as the First Study Treatment Administration month and year.

- For a missing start month:
  - it is assumed to have started on the first of January of that year.
  - or at the date of First Study Treatment Administration if the start year is the same as the First Study Treatment Administration year.

7.3 Study Treatment Groups

A dose finding adaptive approach has been adopted in phase 1 of the study. In the first stage of phase 1, dose administration was to be on Day 1 and Day 15 of each 28-day treatment cycle, whereas in the second stage of phase 1, dose administration was to be on Day1, Day 8 and Day 15 of each 28-day treatment cycle. *In October 2018, the SRC* decided not to proceed into the second stage of phase 1 and *recommended 80 mg/m2 administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle as the dose for Phase 2.*

For the analysis of Phase 1, only the actual dose cohorts are of relevance and these are shown in the below table. Patients are allocated according to the 'Patient Information' eCRF page.

For Phase 1, patient data are summarized under the dose cohort in which they were enrolled. This disregards that *1) after first administration, the Investigator and Sponsor may decide to reduce a patient's dose in case of safety concerns;* or 2) if a patient is receiving study drug by i.v. infusion over a 30-minute time, the patient may change to the 60-minute infusion period if agreed upon by the Sponsor and the Investigator.

Cohort	Dose	Administration	Study Treatment Label
1	60 mg/m^2	30 min infusion, 2 per cycle	60 mg/m^2 in 30 min, 2/cycle
2	80 mg/m^2	30 min infusion, 2 per cycle	80 mg/m^2 in 30 min, 2/cycle
3	100 mg/m^2	30 min infusion, 2 per cycle	100 mg/m^2 in 30 min, 2/cycle
4	60 mg/m^2	60 min infusion, 2 per cycle	60 mg/m^2 in 60 min, 2/cycle
5	80 mg/m^2	60 min infusion, 2 per cycle	80 mg/m^2 in 60 min, 2/cycle
6	100 mg/m^2	60 min infusion, 2 per cycle	100 mg/m^2 in 60 min, 2/cycle

Phase 2 is to recruit *five (5) cohorts with 10 evaluable patients in each cohort expanding to a possible 29 in each cohort under a Simon 2-stage design.*

Five disease cohorts are to recruit patients:

Cohort	Indication	Study Treatment Label
1	Relapsed/refractory small cell lung cancer (SCLC)	Small cell lung cancer
2	Relapsed/refractory soft tissue sarcoma (STS)	Soft tissue sarcoma
3	Relapsed/refractory triple-negative breast cancer (TNBC)	Triple-negative breast cancer
4	Relapsed/refractory ovarian cancer	Ovarian cancer

5	Relapsed/refractory endometrial cancer	Endometrial cancer

Analysis tables for phase 2 are to display the cohorts separately, then a column for the patients of the substudy labelled “Substudy”, and finally results for all cohorts and the substudy combined. Such results are labelled “Total”.

7.4 Analysis Variables

In this section it is described which variables are used for analysis, and it is indicated how they are to be derived (if applicable) and/or how missing values are to be handled, if applicable.

It is noted that protocol deviations are not collected in the eCRF as such. So, these are not part of the analysis.

7.4.1 Disposition

Patients are allocated into analysis populations as defined in section 6.1.

Patients are allocated into treatment cohorts as defined in section 7.3 according to the ‘Patient Information’ eCRF page.

Patient disposition data is collected on the ‘Study Treatment Termination’ eCRF page when a patient completed or discontinued from the study. The Date of completion/discontinuation and the Primary reason for study termination is given in the eCRF. For phase 1 a patient is to be reported as “completed” if they have completed cycle 1. If they start treatment but do not complete the first cycle they are to be documented as ‘Early withdrawal’. For phase 2 a patient is to be reported as “completed” if they have at least one post-baseline Tumor Response Assessment. If they start treatment but do not perform a Tumor Response Assessment they are to be documented as ‘Early withdrawal’.

For patients discontinued, the number of days until discontinuation is defined as

- Date of discontinuation (‘Study Termination’ eCRF page) - date of First Study Treatment Administration +1

For patients completed, the number of days until completion is defined as

- Date of completion (‘Study Termination’ eCRF page) - date of First Study Treatment Administration +1

7.4.2 Inclusion and Exclusion Criteria

The eligibility of all patients for entry into the study is recorded as Yes/No for each individual criterion on the Eligibility Criteria eCRF pages.

7.4.3 Demographic and Other Baseline Characteristics

Demographic information

Demographic information (Date of Birth, Age, Sex, Race and Ethnicity) is recorded at Screening on the ‘Demography’ eCRF page. Age is automatically derived within the eCRF and correspondingly included in the database.

Height (cm) and weight (kg) which is recorded with one decimal precision on the ‘Vital Signs’ eCRF page at Screening, is reported with the demographic information.

Age categories

The following age categories are defined:

- Age < 65 years

- 65 years ≤ age < 75 years
- 75 years ≤ age

BMI

BMI is derived with two decimals precision as

- BMI (kg/m^2) = weight (kg) / (height (m))^2

Baseline Disease Assessment (RECIST)

Baseline Disease Assessment is recorded at screening on the eCRF page 'Baseline Disease Assessment'. For each lesion present, it is recorded: 1) whether it is target/non-target; 2) its location; 3) method of assessment (CT or MRI); 4) date of assessment; 5) size of diameter for target lesions (mm, integer); 6) status for non-target lesions (present or absent). Assigned lesion IDs are unique over all visits within a patient. For patients followed up based on tumour markers the relevant Tumour markers and their current values (Result + Unit) are recorded.

Gene Expression Profiling

If Consent for gene expression is given on the Informed Consent eCRF form, the Gene Expression Profiling eCRF page collects the Type of tissue sample (archival or fresh) and the date and time of the sample.

7.4.4 Cancer History

Cancer history and prior cancer treatments are documented at Screening.

Cancer Diagnosis

On the eCRF page 'Cancer History', data (dates and stages) of the current cancer diagnosis are recorded as well as information of previous cancer diagnosis, if any.

The verbatim diagnosis terms are coded with MedDRA.

Time (years) since current cancer diagnosis is calculated as

- Time since current diagnosis = (Date of First Study Treatment Administration - Date of Current Diagnosis) / 365.25

Time (years) since initial cancer diagnosis is calculated as

- Time since initial diagnosis = (Date of First Study Treatment Administration - Date of Initial Diagnosis) / 365.25

Time (years) since previous cancer diagnosis is calculated as

- Time since previous diagnosis = (Date of First Study Treatment Administration - Date of Previous Diagnosis) / 365.25

Prior Cancer Treatment

On the eCRF page 'Prior Cancer Therapies' the following is collected:

For Prior Systemic Cancer Therapies:

- Previous Treatment [coded with WHO and ATC]
- Line of therapy [integer value indicating the order of therapies]
- Start date, end date, dose and unit, route
- Best response [categories: Complete response, Partial response, Stable disease, No response, Progressive disease, Too early, Not evaluable, Not assessed or Unknown]

For Prior Surgeries Related to Cancer:

- Procedure [coded with MedDRA]
- Anatomical location
- Date of surgery
- Result of surgery [categories: Partial Resection, Complete Resection or Unknown]

For Prior Radiotherapies:

- Location
- Start date, end date, total dose (unit: Gy)
- Best response [categories: Complete response, Partial response, Stable disease, No response, Progressive disease, Too early, Not evaluable, Not assessed or Unknown]

For each patient, the maximum value of line of therapy over all recorded therapies is determined (denoted as line_max).

7.4.5 Other Medical History

On the eCRF page 'Medical History' the following is collected:

- Medical/surgical condition [coded with MedDRA]
- Start date, end date, ongoing (Yes/No)

7.4.6 Prior and Concomitant Medication

Concomitant medications are collected from 30 days prior to the first study drug administration. The 'Prior and Concomitant Therapies' eCRF page collects the following information:

- Trade or generic name [coded with WHO and ATC]
- Start date and time, End date and time, ongoing (Yes/No)
- Route, Dose, Unit, Frequency
- Indication

Medication is classified as 'Prior' if the end date lies before the date of first trial treatment. Else it is regarded as 'Concomitant'. Missing or incomplete dates are handled according to section 7.2.2.

The 'Concomitant Non-Pharmacological Procedure' eCRF page collects the following information:

- Event term [coded with MedDRA]
- Start date and time, End date and time, ongoing (Yes/No)
- Indication

7.4.7 Measurements of Exposure and Treatment Compliance

The Investigator or designee will document the amount of tinostamustine received, the amount dispensed to trial patients and the amount destroyed locally.

Study drug accountability records are maintained throughout the course of the study. On the eCRF page 'Study Drug Administration' it is recorded next to the visit date and the cycle number whether treatment was given and if so, data are completed for:

- dose level (mg/m^2, integer)
- administration date, start time and end time
- body surface area (m^2, 2 decimals precision, Dubois formula)
- Tinostamustine (EDO-S101) Concentration (0.4 mg/mL or 2.0 mg/mL)
- calculated volume (mL, 1 decimal precision)
- administered volume (mL, 1 decimal precision)

as well as reason for interruption/stopping, if applicable.

In case treatment was not given the reason for discontinuation and the relationship (Yes/No) to COVID-19 are documented.

Actual duration of the administration

The actual duration of the tinostamustine administration is calculated as

Calculated duration = end time - start time

Quantity of the study drug

The absolute and relative quantities of the study drug are calculated at the relevant timepoints as follows:

- Calculated Absolute Quantity (mg) = Calculated volume (mL) * Tinostamustine Concentration
- Administered Absolute Quantity (mg) = Administered volume (mL) * Tinostamustine Concentration
- Administered Relative Quantity (mg/m^2) = $\frac{\text{Administered Absolute Quantity (mg)}}{\text{Body Surface Area } (m^2)}$

Where Body Surface Area is as documented on the eCRF page 'Study Drug Administration'.

For each patient, the **Total Administered Volume** (mL), the **Number of Cycles Started** and the **Number of Administrations per Cycle** is calculated straightforward from available eCRF pages. The **Total Administered Absolute Quantity** (mg) and **Total Administered Relative Quantity** (mg/m^2) are calculated as the respective sums over all administrations.

Duration of exposure

The total duration of exposure is calculated as:

Duration of Exposure (days) = (date of Last Study Treatment Administration – date of First Study Treatment Administration + 1)

where date of First Study Treatment Administration is taken from the 'Study Drug Administration' eCRF page of cycle 1 day 1 and date of Last Study Treatment Administration is taken from the Study Termination eCRF page.

Drug Compliance

Patient Drug Compliance in the first cycle is defined as YES if 2 administrations are recorded (on days 1 and 15). Otherwise it is defined as NO.

7.4.8 Efficacy Variables

Response Assessment per assessment visit

Radiologic response assessment by computed tomography (CT) or magnetic resonance imaging (MRI) will be performed at baseline and every two (2) cycles.

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.

Tumor response are evaluated according to RECIST version 1.1. and recorded per assessment visit as a) Complete Response (CR); b) Partial Response (PR); c) Stable Disease (SD); d) Not Evaluable (NE); or e) Progressive Disease (PD). This classification combines the results for target lesions, non-target lesions and new lesions.

On the eCRF page 'Tumor Response Assessment' it is denoted whether the assessment is done and if so, the following is recorded:

For each lesion present, it is recorded: 1) whether it is target/non-target; 2) its location; 3) method of assessment (CT or MRI); 4) date of assessment; 5) size of diameter for target lesions (mm, integer); 6) status for non-target lesions (present or absent). The lesion ID numbers are the same over the baseline and post-baseline visits.

Sum of Lesion Diameters, Shrinkage, Growth

At baseline and all subsequent follow-up RECIST assessments the Sum of Lesion Diameters is defined as

Sum LD = sum (size [mm] of all target lesions).

(For nodal lesions the shortest diameter is to be recorded as "size" otherwise the longest diameter is to be documented.)

If a target lesion is not assessed at a follow-up visit or the size is not documented the last available size is carried forward in order to calculate the sum (LOCF).

RECIST allows for only two lesions per organ to be considered target lesions. If more than two lesions should be documented in one location only those two that are largest at baseline are counted towards the Sum LD even if they should not be the largest two at a later assessment.

For each patient at each follow-up RECIST assessment the following percentages are determined

$$\text{Shrinkage} = 100 * \left(1 - \frac{\text{Sum LD at follow-up}}{\text{Sum LD at baseline}}\right)$$

$$\text{Growth} = 100 * \left(\frac{\text{Sum LD at follow-up}}{\text{lowest Sum LD before follow-up}} - 1\right)$$

Tumor Response Assessment

Further for each assessment the Tumor Response Assessment is recoded as follows:

- Evaluation of target lesions [Complete Response (CR), Partial Response (PR), Stable Disease (SD), Not All Evaluated (NE), Progressive Disease (PD)] as assessed by the investigator and recorded in the eCRF.
- Evaluation of non-target lesions [Complete Response (CR), Incomplete Response / Stable Disease (PR/SD), Not All Evaluated (NE), Progressive Disease (PD)] as assessed by the investigator and recorded in the eCRF.
- New lesions detected [Y, N]
- Automated Overall Response [Complete Response (CR), Partial Response (PR), Stable Disease (SD), Not Evaluable (NE), Progressive Disease (PD)] as derived within the eCRF from the investigator evaluations of target and non-target lesions.
- Investigator's Overall Response [Complete Response (CR), Partial Response (PR), Stable Disease (SD), Not Evaluable (NE), Progressive Disease (PD)]
- Reason for deviation from RECIST

Best Overall Response

Best Overall Response is defined as the best response across all time points based on the Investigator's Overall Responses reported at the assessment visits. The Investigator's Overall

Responses are used without checking for confirmation in a later RECIST assessment. If no follow-up RECIST assessment was performed for a patient during the trial, then Best Overall Response is regarded as missing.

Duration of SD

If a patient's Best Overall Response is SD then the Duration of SD is calculated as

Duration of SD = Date of Progression - Date of First Study Treatment Administration + 1.

The date of progression is defined in section 7.1. If no date of progression is defined for a patient the date of death (as defined in section 7.1) is used as the end date. If neither date of progression nor date of death are recorded for a patient the Duration of SD is censored at the last available RECIST assessment (as defined in section 7.1). If no RECIST assessment was performed during the study after observing SD, the Duration of SD is censored at the Last available visit date (as defined in section 7.1).

Duration of SD categories

For patients with a Best Overall Response of SD Duration of SD is divided into the following categories:

Duration of SD < 84 days

Duration of SD ≥ 84 days

Clinical Benefit Response

The Clinical Benefit Response is set to Yes if the Best Overall Response is CR or PR. It is also set to Yes if the Best Overall Response is SD that has a Duration of SD of at least 84 days (equivalent to 12 weeks). If there is a RECIST assessment of SD with a shorter duration, Clinical Benefit Response is set to No. Also for Best Overall Response of NE and PD Clinical Benefit Response is set to No. If Best Overall Response is missing, Clinical Benefit Response is also missing.

Clinical Benefit Response Rate

The Clinical Benefit Response Rate is calculated as the number of patients with Clinical Benefit Response=Yes divided by number of patients in the FAS (in the respective cohort). Clinical Benefit Response Rate is the primary endpoint.

Objective Response

Objective Response is set to Yes if the Best Overall Response is CR or PR. For SD, NE and PD Objective Response is set to No. If Best Overall Response is missing, Objective Response is also missing.

Objective Response Rate

The Objective Response Rate is calculated as the number of patients with Objective Response=Yes divided by number of patients in the FAS (in the respective cohort).

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 (Cycle 1, Day 1).

At each follow up contact, on the eCRF page 'Survival Follow-up' the follow up status is recorded as a) alive; b) dead (+ date of death); c) lost to follow up; d) not able to obtain any further information; or e) other (+ specification) together with the date of the follow-up contact.

On the eCRF page it is also recorded whether any subsequent anti-cancer therapy had started since last visit and if so, sites are reminded to document this on the eCRF page 'Subsequent Cancer Therapies'.

On the Study Termination Form the Primary Reason for Study Termination can be given as 'Progressive Disease', 'End of observational period/ Patient alive', 'Death' (with 'Date of death'), 'Treatment-emergent adverse event (with 'AE number'), 'Patient's decision' (with specification), 'Investigator's decision' (with specification), 'Termination of the study by the Sponsor' or 'Other' (with specification). Unless the Primary Reason for Study Termination is 'Death' the patient is regarded to be alive at this timepoint. From this information from the Study Termination Form and the latest of the Survival Follow-up forms the status ('Alive', 'Dead', 'Lost to follow up', 'Not able to obtain any further information') is derived. If neither a "Survival Follow-up" nor a "Study Termination" Form are filled in, the status is regarded as "ongoing".

Overall Survival (OS)

Overall survival is defined as the number days between the date of the first dose of treatment and the date of death as defined in section 7.1.

OS = Date of death - Date of First Study Treatment Administration + 1

If no date of death is recorded the Overall Survival time is censored at the Last available visit date (as defined in section 7.1).

Progression Free Survival (PFS)

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.

PFS = Date of progression - Date of First Study Treatment Administration +1

The date of progression is defined in section 7.1. If no date of progression is defined for a patient the date of death (as defined in section 7.1) is used as the event date. If neither date of progression nor date of death are recorded for a patient the PFS is censored at the last available RECIST assessment (as defined in section 7.1). If no RECIST assessment was performed during the study the PFS is censored at the Last available visit date (as defined in section 7.1).

Duration of Response (DoR)

The duration of objective response is measured from the date of the first tumor response assessment with an Investigator's Overall Response of CR or PR (whichever status is recorded first) until the date of progression or death (as defined in section 7.1).

DoR = date of progression - date of first CR/PR + 1

For patients who do not reach CR or PR the duration is set to 0. If no date of progression is defined for a patient the date of death (as defined in section 7.1) is used as the event date. If neither date of progression nor date of death are recorded for a patient the DoR is censored at the last available RECIST assessment (as defined in section 7.1). If no RECIST assessment was performed during the study the DoR is censored at the Last available visit date (as defined in section 7.1).

7.4.9 Safety Variables

Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug 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.

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.

Dose Limiting Toxicity (DLTs)

In phase 1 the assessment for Dose Limiting Toxicity **(**DLTs) is based on Cycle 1 events only. Assessments for DLT occur in the first cycle of each successive dose escalation until the MTD has been determined. *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.*

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 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.*

For the purpose of the analysis any AE marked as DLT on the eCRF is regarded as a Dose limiting toxicity.

AE characteristics

The following data on Adverse Events are recorded on the eCRF page ‘Adverse Events’:

- Event term [coded by MedDRA]
- Serious [Yes/No + 6 options for seriousness criteria: 1-results in death; 2-life-threatening; 3-prolonged hospitalization; 4-persistent/ significant disability/ incapacity; 5-congenital anomaly or birth defect; 6-medically significant]
- Related to infusion process [Yes/No]
- Start date and time, end date and time [data imputation rules in 7.2.2 apply]
- Outcome [recovered/resolved; recovering/resolving; recovered/resolved with sequela; not recovered/not resolved; fatal; unknown]

- CTCAE grade [1 – Mild; 2 – Moderate; 3 – Severe; 4 - Life-threatening; 5 – Death; or 'Not applicable']
- Flag if event meets the definition of a DLT
- Flag if event meets the definition of a DME
- Severity [mild/moderate/severe]
- Relatedness to study drug [Yes/No]
- Action taken with study drug [not changed/ withdrawn/ interrupted/ dose reduced/ dose increased/ unknown/ not applicable]
- Other action taken [none/ specific therapy or medication/ surgical or medical procedure]

Events with unknown or not assessable relatedness to study drug are counted as treatment-related.

Dose Modifying Events (DME)

Dose Modifying Events (DME) are clinically significant toxicities (similar to DLTs) that occur after the first cycle and are marked as such on the AE eCRF page.

For each patient, the number of applicable events with CTCAE grading as well as the maximum CTCAE grade of all applicable events is calculated per cycle.

Treatment Emergent Adverse Event (TEAE)

An AE is regarded as a Treatment Emergent Adverse Event (TEAE) if it occurs on or after the day that treatment is initiated.

TEAE leading to death

A TEAE is regarded as leading to death if the outcome is documented as "fatal".

TESAE

A TEAE is regarded as a TESAE if "Is the event serious?" is answered "yes".

TEAE resulting in treatment discontinuation

A TEAE is regarded as resulting in treatment discontinuation if "Action taken with study drug" .is given as "Study drug withdrawn".

TEAE given as primary reason to terminate treatment

If "Treatment-emergent adverse Event" is given as Primary reason for study termination on the Study Treatment Termination eCRF page the specified "AE number" identifies the TEAE given as primary reason to terminate treatment.

TEAE 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.

TEAEs of special interest are identified by the MedDRA PT code "Electrocardiogram QT prolonged".

Infusion Site and Allergic Reaction Assessment

All injection site reactions will be considered AEs. 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.

On the eCRF page 'Infusion Site and Allergic Reaction Assessment' at each scheduled time point the 24 hours clock time is recorded, whether abnormalities are observed [Yes, No] or assessment not done and if not done, the reason why the assessment is not done as well as if the reason for not doing the assessment is related to Covid-19 [Yes/No].

Pregnancy Testing

A serum or urine pregnancy test will be performed for female patients of childbearing potential. A positive urine pregnancy test result observed following enrollment should be confirmed with a repeat serum pregnancy test.

Pregnancy test results are recorded on the eCRF page 'Serum/Urine pregnancy Test'.

The Investigator must obtain consent to collect pregnancy information (including the status of the newborn, if applicable). 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. These data are not included in the study database, neither in the statistical analysis nor in the study report.

ECOG Performance Status

ECOG performance status of each patient is 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 defined in the below table.

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*

If the ECOG status at the Study Discontinuation visit is not documented the last available post-baseline (ie. post C1D1) ECOG status is determined instead for use in the summary table described in section 10.7.4.

Laboratory variables

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). 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). 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.

Within the data base lab values of hematology and chemistry are converted to standard units. For summary tables these converted values are used.

Laboratory categories based on modified CTCAE Grades

The following laboratory parameters are divided into categories as per CTCAE version 4.03: The lowest grade has been modified to include values below LLN

White blood cell count (WBC) x10^3/uL

Grade 0/1: > 3.0 x 10^3 /uL

Grade 2: <3.0 x 10^3 /uL - 2.0 x 10^3 /uL

Grade 3: <2.0 x 10^3 /uL - 1.0 x 10^3 /uL

Grade 4: <1.0 x 10^3 /uL

Neutrophils

Grade 0/1: > 1.5 x 10^3 /uL

Grade 2: <1.5 x 10^3 /uL - 1.0 x 10^3 /uL

Grade 3: <1.0 x 10^3 /uL - 0.5 x 10^3 /uL

Grade 4: < 0.5 x 10^3 /uL

Lymphocytes

Grade 0/1: > 0.8 x 10^3 /uL

Grade 2: < 0.8 - 0.5 x 10^3 /uL

Grade 3: <0.5 - 0.2 x 10^3 /uL

Grade 4: <0.2 x 10^3 /uL

Platelets

Grade 0/1: > 75.0 x 10^3 /uL

Grade 2: <75.0 x 10^3 /uL - 50.0 x 10^3 /uL

Grade 3: <50.0 x 10^3 /uL - 25.0 x 10^3 /uL

Grade 4: <25.0 x 10^3 /uL

For each of the parameters the worst (highest) grade over all post-baseline assessments is determined per patient. If Lymphocytes or Neutrophils are given as a percentage they are converted into absolute values as follows:

Absolute value (in 10^3 /uL) = (percentage value / 100) * WBC (in 10^3 /uL)

Vital Signs / Weight and Height

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.

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.

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 complete physical examination will include:

- *General appearance*
- *Head, eyes, ears, nose, and throat*
- *Respiratory*
- *Cardiovascular*
- *Musculoskeletal*
- *Abdomen*
- *Neurologic*
- *Extremities*
- *Dermatologic*
- *Lymphatics*

ECG variables

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. The analysis of these Holter data falls outside the scope of this SAP.

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

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.

From the eCRF page '12-lead ECG Assessments' in addition to the date and time of assessment, the following variables are databased in integer values: Heart Rate (HR (bpm)), PR (msec), QRS (msec), QT (msec), QTcB (msec) (partially for some of the phase 1 patients) and QTcF (msec) (not available for some phase 1 patients). Also the Investigator's Interpretation (Normal, Abnormal/Not-Clinically-Significant, Abnormal/Clinically Significant) is recorded together with possible specifications of the abnormality.

Mean of Triplicate QTcF

At each timepoint where a triplicate ECG is to be measured the arithmetic mean of the QTcF measurements is calculated and used for summary statistics.

QTcF Change from Pre-Cycle

Within each cycle a Change from Pre-Cycle is calculated for QTcF relative to the pre-dose value of day 1 of the cycle.

QTcF Change from Pre-Cycle = QTcF Post-dose value - QTcF Pre-Dose value of D1

At timepoints with triplicate ECG measurements the Mean of Triplicate QTcF is used for the calculation.

QTcF highest increase

The QTcF highest increase is defined as the highest QTcF Change from Pre-Cycle over all cycles.

QTcF highest increase categories

QTcF highest increase is categorised as follows

QTcF highest increase ≥ 30 msec

QTcF highest increase ≥ 60 msec

Patients counted in the ≥ 60 msec category are also counted in the ≥ 30 msec category.

Pharmacokinetics, Gene Expression

The analysis of data related to Pharmacokinetics (PK) and Gene Expression falls outside the scope of this SAP.

8. Analysis Methods

8.1 General Methods

For continuous variables the mean, standard deviation, minimum, median and maximum are presented together with the total number of observations and the number of missing and non-missing values. Unless otherwise specified minimum and maximum values are reported to the same number of decimal places as the recorded measurements, mean and median are reported to one more decimal place and standard deviation one additional decimal place more than the mean.

For categorical variables, absolute and relative frequencies are reported. Relative frequencies are based on all observations and reported as percentages to one decimal place. Unless otherwise specified (which is mostly for event data) percentages are based on the number of patients with data and are not calculated for missing categories.

Adverse events, medical histories and concomitant medications are reported on a patient basis. The percentages are calculated using the number of patients in the Safety Analysis Set as the denominator.

All summary tables are presented separately by treatment cohort (phase 1) or disease cohort (phase 2) and per cycle and cycle day unless specified otherwise. The data of the substudy are presented together with the phase 2 data but treated as a separate cohort. Summary tables are based on the SAF unless specified otherwise.

All data collected are presented in listings. These listings are based on the SAF unless specified otherwise, and by default include the patient identification [4+3]-digit patient number.

Post-Text TLFs are provided in collated electronic MS Word .rtf files.

8.2 Specific Methods for Efficacy Analyses

Exact 90% confidence intervals for rates/proportions are determined following the exact Clopper-Pearson method. Absolute and relative frequencies for events/non-events as well as the total number of valid observations are reported together with the estimated event rate and the lower and upper limits of the confidence interval.

For Survival analyses, results from a Kaplan-Meier analysis (PROC LIFETEST) are shown, including Survival rate, failure rate (=1 – Survival rate), Survival standard error, Number of patients failed (cumulative), number of patients left and patient ID. Graphical presentation are given, with survival rate on the vertical axis (0.00 to 1.00) and time to event (failure) on the horizontal axis. Median survival time is presented with 90% Confidence Interval, as well as Q1 and Q3 survival times.

8.2.1 Statistical/Analytical Issues for Efficacy Analyses

8.2.1.1 Adjustments for Covariates

Not applicable

8.2.1.2 Handling of Dropouts or Missing Data

For incomplete dates date part imputation is performed as defined in section 7.2.2.

For the calculation of Sum LD Last Observation Carried Forward (LOCF) is applied as described in section 7.4.8.

8.2.1.3 Blind Review

Not applicable since this is an open label study.

8.2.1.4 Multicentre Studies

All data are presented pooled over all centers and over all tumor types.

8.2.1.5 Multiple Comparisons/Multiplicity

No account for multiple comparisons or multiple testing is made.

8.3 Specific Methods for Safety Analyses

Not applicable.

8.4 Specific Methods for Pharmacokinetic Analyses

Not applicable.

8.5 Specific Methods for Pharmacodynamic Analyses

Not applicable.

8.6 Specific Methods for Pharmacoeconomic Analyses

Not applicable.

9. Interim analyses

Four analyses are performed as follows:

1. Interim analysis after completion of the dose escalation part of the study in order to provide input to a RP2D Decision Report. The selection of included clinical domains as well as the adopted statistical analysis methods follows the related instructions as provided by Mundipharma Research limited. No significance tests are performed during this interim analysis. Therefore no adjustment of Type 1 error needs to be considered. This analysis is performed on the Total Set (TOT) and/or Safety Analysis Set (SAF) only and includes follow up data up to an agreed cut-off date.
2. At the end of the Substudy a summary safety report is produced. The selection of included clinical domains follows the instructions as provided by Mundipharma Research limited. No significance tests are performed during this interim analysis. Therefore, no adjustment of Type 1 error needs to be considered.
3. For each disease cohort, at the end of stage 1 of the Simon-Two-Stage design, a summary report is produced as soon as a decision on success or failure (Clinical Benefit Response) can be determined for all of the first 10 patients of the first stage. The selection of included clinical domains follows the instructions as provided by Mundipharma Research limited. No significance tests are performed during this interim analysis. Therefore, no adjustment of Type 1 error needs to be considered.
4. Final analysis of the full study according to the study protocol after completion of the dose expansion part of the study.

10. Overview of Tables, Listings and Figures

In this section, TLFs are presented content wise. The full set of TLFs is tabulated in section 12, where it is indicated whether the item is unique (or first mentioned) or a repeat. Mock shells for unique TLFs are presented in a separate document.

Separate sets of output are produced for phase 1 and phase 2. Safety tables combining all patients of the RP2D cohort are displayed within the phase 2 set of outputs. Unless otherwise stated TLFs are produced on the SAF.

10.1 Disposition of Patients

A table summarizes the disposition of patients for the Total Set (number of patients who completed and discontinued the study). All percentages are based on the number of patients treated. This table also presents the summary statistics for the primary reasons for study termination.

A table presents the summary statistics for the number of days until discontinuation for patients of the SAF who discontinued the study.

A table presents the summary statistics for the number of days until completion for patients of the SAF who completed the study.

A listing presents the informed consent date, the study completion data, including the primary reason for study termination as given in the eCRF as ‘Progressive Disease’, ‘End of observational period/ Patient alive’, ‘Death’ (+ Date of death, Day of death), ‘Treatment-emergent adverse event’ (+ AE number), ‘Patient’s decision’ (+ Specification), ‘Investigator’s decision’ (+ Specification), ‘Termination of study by the sponsor’ or ‘Other’ (+ Specification) for the Total Set.

10.2 Protocol Deviations

10.2.1 Inclusion and Exclusion Criteria

Listings present all patients who failed to meet at least one of the Inclusion or Exclusion criteria, along with all the failing Inclusion and Exclusion responses for the Total Set.

10.3 Data Sets Analysed

A table gives an overview of the number of patients per treatment cohort (phase 1) or disease cohort (phase 2) in each analysis set as defined in section 6.1.

A listing presents the allocation of each patient to the respective analysis sets.

10.4 Demographic and Other Baseline Characteristics

10.4.1 Demographic Characteristics

A table presents the summary statistics for demographic data, augmented with height, weight and BMI at screening, including collected and derived variables.

A listing presents all collected and derived demographic data.

10.4.2 Baseline Disease Characteristics

Two listings present all baseline disease assessment data. For patients followed up per lesions Lesion ID, Target/Non-Target, Location, Method of assessment (CT/ MRI), Date of

assessment, Size and Status are listed. For patients followed up based on tumour markers the Tumour marker (Name of marker/ Other (Specification)), Result and Unit are listed.

A listing presents the Date of consent for gene expression (or 'Not given'), the Type of tissue sample (Archival Tissue Sample, Fresh Tissue Sample or Not done), Sampling Date and Time.

10.4.3 Cancer History

A listing presents all current cancer diagnosis data: Current cancer diagnosis (MedDRA SOC, PT, Verbatim), Date of current diagnosis, Time since current cancer diagnosis (years), Stage at study entry, Date of initial diagnosis, Time since initial cancer diagnosis (years), Stage at initial diagnosis, History of cancer other than current cancer? (Y/ N).

A listing presents all previous cancer diagnosis data: Previous Cancer Diagnosis (MedDRA SOC, PT, Verbatim), Date of diagnosis, Time since previous cancer diagnosis (years), Stage at initial diagnosis, Ongoing (Yes/No).

A table presents the number and percentages of patients who had at least one prior systemic, surgical or radio cancer therapy on the SAF.

A table presents the number and percentages of overall highest line of therapy (observed line_max values) on the SAF.

A listing presents all prior systemic cancer therapy data, including coded data.

A listing presents all prior surgery data related to cancer, including coded data.

A listing presents all prior radiotherapy data, including coded data.

10.4.4 Other Medical History

A listing presents all Medical History data: Medical/surgical condition (MedDRA SOC, PT, Verbatim), Start date, end date (or "ongoing").

Medical History data are summarised on a per-event and on a per-patient basis (i.e., if a patient reported events of the same MedDRA category repeatedly the patient is counted only once at the specific level of display). Absolute counts (n) and percentages (%) are presented for the number of patients with at least one Medical History event, and per SOC and per PT within SOC. Percentages are based on the number of patients in the population.

10.4.5 Prior and Concomitant Medications and Procedures

A listing presents all prior and concomitant medication data: Medication number, Start date/ time, End date/time (or 'ongoing'), Classification (Prior/Concomitant), ATC Chemical Subgroup, Verbatim, Route, Dose, Unit, Frequency, Indication (including number of MH or AE item).

Another listing presents concomitant non-pharmacological procedures: Procedure number, Event term/PT/SOC, Start date and time, End date and time (or 'ongoing') and Indication (including number of MH or AE item).

Concomitant Medications are summarised on a per-event and on a per-patient basis (i.e., if a patient reported medications of the same ATC or WHO category repeatedly the patient is counted only once at the specific level of display). Absolute counts (n) and percentages (%) are presented for the number of patients with at least one Concomitant Medication, and per ATC level (Anatomical Main Group, Therapeutic Subgroup, Chemical subgroup) and per Preferred Name within ATC. Percentages are based on the number of patients in the population.

10.5 Measurement of Exposure and Treatment Compliance

A table presents the summary statistics for Total Administered Volume (ml), the Total Administered Absolute Quantity (mg), the Total Administered Relative Quantity (mg/m^2), the Number of Cycles Started and Duration (days) of Exposure on the SAF.

A table presents the number and percentage of patients who are treatment compliant in the first cycle on the SAF.

A listing presents all collected and derived drug accountability data per administration day (Cycle, Day, Treatment given? (Yes/No (Reason for discontinuation, Related to COVID-19?)), Admin. date, Start time/ End time, Dose Level (mg/m^2), Calculated duration (min), Body Surface Area (m^2), Calc. volume (mL), Calculated Absolute Quantity (mg), Admin. vol. (mL), Admin. Absolute Quantity (mg), Admin. Relative Quantity (mg/m^2), Treatment interrupted/ stopped? (Reason)).

Another listing presents the derived exposure data per patient over the course of the study (Total Administered Volume (mL), Total Administered Absolute Quantity (mg), Total Administered Relative Quantity (mg/m²), Number of Cycles Started, Duration of Exposure (days), Drug Compliance in First Cycle (Yes/No)).

10.6 Efficacy Results

10.6.1 Primary Efficacy Analysis – RECIST assessment

A table presents the summary statistics for “Automated Overall Response" and the "Investigators Overall Response" at subsequent assessments, i.e., they are summarised for "1st FU assessment", "2nd FU assessment" etc. on the FAS.

For phase 2 a table presents the summary statistics for Best Overall Response (CR, PR, SD, PD, NE, missing), the Duration of SD categories, the Clinical Benefit Response Rate with corresponding confidence interval as well as the Objective Response Rate with corresponding confidence interval on the FAS. Clinical Benefit Response Rate is the primary endpoint.

A listing presents for all target and non-target lesions, per lesion ID all collected data on available RECIST assessments.

A listing presents all collected overall response assessments (Automated and Investigator’s) as well as the calculated Sum LD, shrinkage and growth data per RECIST assessment. Sum LD calculated using LOCF is marked as such.

A listing presents the Best Overall Response, Duration of SD, the Clinical Benefit Response and the Objective Response.

10.6.2 Secondary Efficacy Analysis

10.6.2.1 Survival Follow-up

A table presents the summary statistics for the latest follow up status on the SAF.

A listing presents the collected survival follow up data.

Three listings present the collected data on subsequent systemic cancer therapies, subsequent surgeries and subsequent radiotherapies.

A listing presents the times to Overall Survival, Progression Free Survival and Duration of Response. Censored times are marked as such.

10.6.2.2 Overall Survival

A Kaplan-Meier analysis is performed on the Overall Survival data of the FAS population of phase 2 as described in section 8.2. Figures present the Kaplan-Meier graphs of each cohort and of the overall FAS population. A table presents the number of patients with event death, the number of patients with censoring, the median survival time with its 90% Confidence Interval, as well as Q1 and Q3 survival times.

10.6.2.3 PFS

A Kaplan-Meier analysis is performed on the Progression Free Survival data of the FAS population of phase 2 as described in section 8.2. Figures present the Kaplan-Meier graphs of each cohort and of the overall FAS population. A table presents the number of patients with event progression, the number of patients with event death, the number of patients with censoring, the median survival time with its 90% Confidence Interval, as well as Q1 and Q3 survival times.

10.7 Safety Results

All safety results are analysed on the Safety Analysis Set (SAF). Data for phase 1 and phase 2 are presented separately. *For Phase 1, patient safety data are summarized under the dose cohort in which they were enrolled. For Phase 2, patient safety data are summarized by disease cohort as well as over all disease cohorts. 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.* For this, patients from the 80 mg/m^2 (60 minutes infusion) treatment cohort of phase 1 are combined with the phase 2 patients. This is done for all disease cohorts combined and where indicated below.

10.7.1 Adverse Events

Brief Summary of Adverse Events

A table summarizes the AEs (including the number of patients with at least one AE, at least one TEAE, at least one Serious TEAE, at least one TEAE leading to death, at least one DLT, at least one DME, the number of patients with a TEAE resulting in treatment discontinuation, with at least one TEAE of special interest, TEAEs by the worst CTCAE Grade of any TEAE experienced by each patient with at least one TEAE and number of patients with at least one related TEAE). Additionally, to being displayed for phase 1 and phase 2 separately, the above analysis is repeated for all patients of phase 1 and phase 2 combined who were recruited on the RP2D and schedule.

A table presents summary statistics for number of CTCAE graded events.

Display of Adverse Events

Treatment Emergent Adverse Events are summarised on a per-event and on a per-patient basis (i.e., if a patient reported events of the same MedDRA category repeatedly the patient is counted only once at the specific level of display). Absolute counts (n) and percentages (%) are presented for the number of patients with at least one Treatment Emergent Adverse Event, and per SOC and per PT within SOC. Percentages are based on the number of patients in the population.

Descriptive tables are ordered by descending frequency of the overall number of patients within each SOC and then ordered within each SOC by the overall number of patients within each PT and the overall number of events within each PT. In the event of equal frequencies tables are ordered alphabetically.

TEAEs are summarized in occurring subsets of events as follows:

- Treatment-Related TEAEs
- TEAEs by Worst CTCAE Grade
- Serious TEAEs
- TEAEs leading to death
- TEAEs that Led to Permanent Withdrawal of Study Drug
- TEAEs Given as Primary Reason to Terminate Treatment
- TEAEs leading to dose reduction, interruption or discontinuation

Additionally to being displayed for phase 1 and phase 2 separately, the above analyses are repeated for all patients of phase 1 and phase 2 combined who were recruited on the RP2D and schedule.

Listing of Adverse Events

Listings present all recorded Adverse Event data (raw and derived), including flags for DLT, DME, relatedness to infusion process and MedDRA PT and SOC, and ordered within patient by onset date and time and end date and time of the event. One listing presents Pre-treatment AEs for the Total Set, another listing presents TEAEs on the Safety Analysis Set.

Serious Adverse Events

A listing presents all Adverse Event data (raw, derived, and coded, equivalent to the format for the AE listings) ordered within patient by onset date and time and end date and time of the event, for Treatment-Emergent Serious AEs.

Deaths

A listing presents all Adverse Event data (raw, derived, and coded, equivalent to the format for the AE listings) ordered within patient by onset date and time and end date and time of the treatment-emergent events with outcome Death.

Dose Limiting Toxicities

A listing presents all Adverse Event data (raw, derived, and coded, equivalent to the format for the AE listings) ordered within patient by onset date and time and end date and time of the event, for TEAEs marked as considered to be a DLT.

Dose Modifying Events

A listing presents all Adverse Event data (raw, derived, and coded, equivalent to the format for the AE listings) ordered within patient by onset date and time and end date and time of the event, for TEAEs marked as considered to be a DME.

Events of Special Interest

A listing presents all Adverse Event data (raw, derived, and coded, equivalent to the format for the AE listings) ordered within patient by onset date and time and end date and time of the event, for TEAEs of special interest.

10.7.2 Infusion Site and Allergic Reaction Assessment

A table presents per scheduled time point per visit the number and percentage of patients that have reported abnormalities at injection site.

A listing presents the collected injection site assessment data.

10.7.3 Pregnancy Testing

A listing presents visit wise per patient, all collected pregnancy test data for the Total Set.

10.7.4 ECOG performance status

A table presents the number and percentage of patients for all six ECOG grades at screening and at study completion/discontinuation visit. Additionally, a shift table between the said visits is presented.

A listing presents the collected ECOG data.

10.7.5 Clinical Laboratory Evaluation

Separate listings for hematology, chemistry and urinalysis present the raw values and their normal ranges. Listings for hematology and chemistry also contain the values converted to standard units as provided from the data base.

Separate tables for hematology and chemistry present the descriptive statistics for continuous variables as described in section 8.1 per visit on the SAF.

For the following laboratory parameters shift tables are produced comparing baseline (C1D1) with the worst post-baseline grade on the SAF: WBC, Neutrophils, Lymphocytes, Platelets.

10.7.6 Vital Signs

Vital Signs are presented in a listing presenting all raw values.

A table presents the descriptive statistics of the Vital Signs as per continuous variables as described in section 8.1 per visit on the SAF.

10.7.7 Physical Examination

Results of the Physical examination are presented in a listing.

10.7.8 ECGs

A table presents summary statistics for Investigator Interpretation per time point per visit.

A table presents the descriptive statistics for QTcF and the QTcF Change from Pre-Cycle at all scheduled timepoints. For timepoints with triplicate ECG measurements the Mean of Triplicate QTcF is presented. QTcF is analysed as a continuous variable as described in section 8.1 on the SAF.

A table presents descriptive statistics for QTcF highest increase on the SAF. QTcF highest increase is analysed as a continuous variable as described in section 8.1. The same table presents the QTcF highest increase categories.

A listing presents all collected ECG data (HR, PR, QRS, QT, QTcB, QTcF and Investigator assessment).

11. References

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228–247

Simon R (1989). “Optimal Two-Stage Designs for Phase II Clinical Trials.” Controlled Clinical Trials 10: 1-10.

12. Tables, Listings and Figures

In the rightmost column it is indicated whether the item is U=Unique TLF (or first instance of a table to be repeated) or R=Repeat item.

"Ph1": outputs for phase 1 patients. "Ph2": outputs for phase 2 patients. Tables marked with an asterisk in the "Ph2" column are produced for all phase 2 patients (by cohort as usual) and additionally pooled for patients of the 80 mg/m^2 (60 minutes infusion) treatment cohort of phase 1 and all patients of phase 2 in one combined "RP2D Overall" cohort.

12.1 Post-Text Tables

In agreement with Medical Writing, numbering of the actual output is produced in format T-14.A-x.y where A is 1, 2, 3 etc. as per ICH-E3 guideline as indicated below and x.y as indicated in the 2nd column of the below table.

Section in SAP	TLF number T (14.A-) x.y	Title	Sample	Ph1	Ph2	U / R
14.1 Demographic Data and other Baseline Characteristics						
10.1	T 1.1	Summary of Patient Disposition	TOT	x	x	U
	T 1.2	Summary of Number of Days until discontinuation for early discontinuations	SAF	x	x	U
	T 1.3	Summary of Number of Days until completion for completers	SAF	x	x	R
10.3	T 2.1	Summary of Analysis Sets	TOT	x	x	U
10.4.1	T 3.1	Summary of Demographic Characteristics	SAF	x	x	U
10.4.3	T 5.1	Summary of Prior Cancer Therapy	SAF	x	x	U
	T 5.2	Summary of the Overall Highest Line of Prior Cancer Therapy	SAF	x	x	U
10.4.4	T 6.1	Summary of Medical History by System Organ Class and Preferred Term	SAF	x	x	U
10.4.5	T 7.1	Summary of Concomitant Medications by ATC and WHO Preferred Name	SAF	x	x	U
10.5	T 8.1	Summary of Exposure	SAF	x	x	U
	T 8.2	Summary of Treatment Compliance in first cycle	SAF	x	-	U
14.2 Efficacy Data						
10.6.1	T 1.1	Summary of Tumor Response (RECIST)	SAF	x	x	U
	T 1.2	Summary of Best Overall Response and Response Rates	FAS	-	x	U
10.6.2.1	T 2.1	Summary of Latest Survival Follow-up	SAF	x	x	U
10.6.2.2	T 3.1	Summary of Overall Survival	FAS	-	x	U

Section in SAP	TLF number T (14.A-) x.y	Title	Sample	Ph1	Ph2	U / R
10.6.2.3	T 4.1	Summary of Progression Free Survival	FAS	-	x	R
14.3 Safety Data						
10.7.1	T 1.1	Summary of Adverse Events, including DLTs	SAF	x	x*	U
	T 1.2	Summary of CTCAE Graded Adverse Events	SAF	x	x*	U
	T 1.3	Summary of Number of Events and Number of Patients with Treatment Emergent Adverse Events by System Organ Class and Preferred Term	SAF	x	x*	U
	T 1.4	Summary of Number of Events and Number of Patients with Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	SAF	x	x*	R
	T 1.5	Summary of Number of Events and Number of Patients with Treatment Emergent Adverse Events by Worst CTCAE Grade, System Organ Class and Preferred Term	SAF	x	x*	R
	T 1.6	Summary of Number of Events and Number of Patients with Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	SAF	x	x*	R
	T 1.7	Summary of Number of Events and Number of Patients with Treatment Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term	SAF	x	x*	R
	T 1.8.1	Summary of Number of Events and Number of Patients with Treatment-Emergent Adverse Events that led to permanent withdrawal of the study drug by System Organ Class and Preferred Term	SAF	x	x*	R
	T 1.8.2	Summary of Number of Events and Number of Patients with Treatment-Emergent Adverse Events Given as Primary Reason to Terminate Treatment by System Organ Class and Preferred Term	SAF	x	x*	R
	T 1.9	Summary of Number of Events and Number of Patients with Treatment Emergent Adverse Leading to Dose Reduction, Interruption or Discontinuation by System Organ Class and Preferred Term	SAF	x	x*	R
10.7.2	T 2.1	Summary of Abnormalities at Injection Site	SAF	x	x	U
10.7.4	T 3.1	Summary of ECOG	SAF	x	x	U
	T 3.2	Shift Table of ECOG	SAF	x	x	U
10.7.5	T 4.1	Summary of Hematology Laboratory Parameters	SAF	x	x	U
	T 4.2	Summary of Chemistry Laboratory Parameters	SAF	x	x	R
	T 4.3	Shift table of Laboratory CTCAE grades	SAF	x	x	U

Section in SAP	TLF number T (14.A-) x.y	Title	Sample	Ph1	Ph2	U / R
10.7.6	T 5.1	Summary of Vital Signs Parameters	SAF	x	x	U
10.7.8	T 7.1	Summary of Investigator Interpretation of ECG per time point per visit	SAF	x	x	U
	T 7.2	Summary of QTcF	SAF	x	x	U
	T 7.3	Summary of QTcF Highest Increase	SAF	x	x	U

12.2 Post-Text Figures

In agreement with Medical Writing, numbering of the actual output is produced in format F-14.A-x.y where A is 1, 2, 3 etc. as per ICH-E3 guideline as indicated below and x.y as indicated in the 2nd column of the below table.

Section in SAP	TLF number T (14.A-) x.y	Title	Sample	Ph1	`Ph2	U / R
14.2 Efficacy Data						
10.6.2.2	F 3.1	Kaplan-Meier Curve for Overall Survival	FAS	-	x	U
10.6.2.3	F 4.1	Kaplan-Meier Curve for Progression Free Survival	FAS	-	x	R

12.3 Post-Text Listings

In agreement with Medical Writing, numbering of the actual output is produced in format T-16.2.A-x.y where A is 1, 2, 3 etc. as per ICH-E3 guideline as indicated below and x.y as indicated in the 2nd column of the below table.

Section in SAP	TLF number L (16.2.A-) x.y	Title	Sample	Ph1	Ph2	U / R
16.2.1 Discontinued patients						
10.1	L 1	Listing of Study Completion with Reason for Termination	TOT	x	x	U
16.2.2 Protocol deviations						
10.2	L 1	Listing of Patients who fail to meet at least one Inclusion Criterion	TOT	x	x	U
	L 2	Listing of Patients who fail to meet at least one Exclusion Criterion	TOT	x	x	R
16.2.3 Patients excluded from the efficacy analysis						
10.3	L 1	Listing of Patients Analysis Sets	TOT	x	x	U

Section in SAP	TLF number L (16.2.A-) x.y	Title	Sample	Ph1	Ph2	U / R
16.2.4 Demographic data and other baseline characteristics						
10.4.1	L 1	Listing of Demographic Characteristics	SAF	x	x	U
10.4.2	L 2.1	Listing of Baseline Disease Assessments - Lesions	SAF	x	x	U
	L 2.2	Listing of Baseline Disease Assessments - Tumor markers	SAF	x	-	U
	L 2.3	Listing of Gene Expression Sampling	SAF	x	x	U
10.4.3	L 3.1	Listing of Current Cancer Diagnosis	SAF	x	x	U
	L 3.2	Listing of Previous Cancer Diagnosis	SAF	x	x	R
	L 3.3	Listing of Prior Systemic Cancer Therapy	SAF	x	x	U
	L 3.4	Listing of Prior Surgery Related to Cancer	SAF	x	x	U
	L 3.5	Listing of Prior Radiotherapy	SAF	x	x	U
10.4.4	L 4	Listing of Other Medical History	SAF	x	x	U
10.4.5	L 5.1	Listing of Prior and Concomitant Medication	SAF	x	x	U
	L 5.2	Listing of Concomitant Non-Pharmacological Procedures	SAF	x	x	U
16.2.5 Compliance and/or drug concentration data						
10.5	L 1	Listing of Study Drug Administration	SAF	x	x	U
	L 2	Listing of Exposure and Treatment Compliance	SAF	x	x	U
16.2.6 Individual efficacy response data						
10.6.1	L 1.1	Listing of Lesion Assessments	SAF	x	x	U
	L 1.2	Listing of Tumor Response Assessments	SAF	x	x	U
	L 1.3	Listing of Tumor Response	SAF		x	U
10.6.2.1	L 2.1	Listing of Survival Follow-up	SAF	x	x	U
	L 2.2	Listing of Subsequent Systemic Cancer Therapy	SAF	x	x	R
	L 2.3	Listing of Subsequent Surgeries Related to Cancer	SAF	x	x	R
	L 2.4	Listing of Subsequent Radiotherapy	SAF	x	x	R
	L 2.5	Listing of Time-to-event Data	SAF	-	x	U
16.2.7 Adverse event listings						
10.7.1	L 1	Listing of Pre-Treatment Adverse Events	TOT	x	x	U
	L 2	Listing of Treatment Emergent Adverse Events	SAF	x	x	R
	L 3	Listing of Treatment-Emergent Serious Adverse Events	SAF	x	x	R

Section in SAP	TLF number L (16.2.A-) x.y	Title	Sample	Ph1	Ph2	U / R
	L 4	Listing of Treatment Emergent Adverse Events with Outcome Death	SAF	x	x	R
	L 5	Listing of Dose Limiting Toxicities	SAF	x	x	R
	L 6	Listing of Dose Modifying Events	SAF	x	x	R
	L 7	Listing of Treatment Emergent Adverse Events of Special Interest	SAF	x	x	R
16.2.8. Listing of laboratory measurements and other safety parameters						
10.7.2	L 1	Listing of Infusion Site and Allergic Reactions	SAF	x	x	U
10.7.3	L 2	Listing of Pregnancy Assessments	TOT	x	x	U
10.7.4	L 3	Listing of ECOG assessments	SAF	x	x	U
10.7.5	L 4.1	Listing of Hematology Laboratory Parameters	SAF	x	x	U
	L 4.2	Listing of Chemistry Laboratory Parameters	SAF	x	x	R
	L 4.3	Listing of Urinalysis Laboratory Parameters	SAF	x	x	U
10.7.6	L 5	Listing of Vital Signs	SAF	x	x	U
10.7.7	L 8	Listing of Physical Examinations	SAF	x	x	U
10.7.8	L 7	Listing of ECG	SAF	x	x	U

13. Appendices

Not applicable