1. TITLE PAGE

CLINICAL STUDY REPORT

Note: This report only presents the data from Phase 1 part of the study. Phase 2 part is ongoing at the time of writing this report.

FULL VERSION FOR REGULATORY USE

STUDY TITLE: A PHASE 1/2 STUDY TO INVESTIGATE THE SAFETY, PHARMACOKINETICS AND EFFICACY OF EDO-S101, A FIRST-IN-CLASS ALKYLATING HISTONE DEACETYLASE INHIBITION (HDACI) FUSION MOLECULE, IN PATIENTS WITH ADVANCED SOLID TUMORS

Test Product: Tinostamustine (EDO-S101)

Sponsor's Responsible Medical Officer name and qualifications:
Katarina Hilgier, MD.

Sponsor name and address:

(Until 23-Jan-2020)
Mundipharma-EDO GmbH
St Alban Rheinweg 74 CH 4052 Basel

(After 24-Jan-2020)
Mundipharma Research Limited
Cambridge Science Park, Milton Road, Cambridge CB4 0AB

Sponsor's Signatory name and position:

Katarina Hilgier, MD. Medical Monitor	K Hilgier Signature	17. 12. 2022 Date (dd-mmm-yyyy)
Nick Manamley, MSc. Head of Biometrics	Nick Manamley Signature Digitally signed by Nick Manamley Date: 2022.12.19 19:22:21 Z	..... Date (dd-mmm-yyyy)

Protocol Number: EDO-S101-1002
Trial Registry name and number: ClinicalTrials.gov NCT03345485
IND Number: 125180
EudraCT Number: Not applicable
Study Phase: Phase 1/2

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice, including the archiving of essential documents.

Version 1, 16 December 2022

Company name: Mundipharma Research Limited **Study number: EDO-S101-1002**
Test product: Tinostamustine (EDO-S101) **CSR Version 1, 16 December 2022**

2. SYNOPSIS

NAME OF SPONSOR: Mundipharma-EDO GmbH (until 23-Jan-2020), Mundipharma Research Limited (after 24-Jan-2020)
NAME OF FINISHED PRODUCT: not applicable
NAME OF ACTIVE INGREDIENT: Tinostamustine (EDO-S101)
TITLE OF STUDY: A Phase 1/2 Study to Investigate the Safety, Pharmacokinetics and Efficacy of EDO-S101, a First-in-Class Alkylating Histone Deacetylase Inhibition (HDACi) Fusion Molecule, in Patients with Advanced Solid Tumors **PROTOCOL NUMBER:** EDO-S101-1002
PRINCIPAL INVESTIGATOR NAME (Phase 1): Shivaani Kummar, MD, FACP. Stanford School of Medicine, Palo Alto, CA **NUMBER OF STUDY CENTRES AND COUNTRIES (Phase 1):** 3 centres in the United States
PUBLICATION (REFERENCES): Mita A, et al. European Society of Medical Oncology (ESMO) Congress 2019. 27 Sep - 1 Oct 2019. Barcelona, Spain. Poster #4264; Mita A, et al. American Association for Cancer Research (AACR) Annual Meeting 2019. 29 Mar - 3 Apr 2019. Atlanta USA, Poster #CT023
STUDY PERIOD (Phase 1): Date of First Subject First Dose: 08-Nov-2017 Date of Phase 1 Completion: October 2018 Date of Last Subject Last Follow-up: 15-Jul-2020
REPORTING PERIOD (Phase 1): Date of First Data Collection: 18-Oct-2017 Date of Last Data Collection: 15-Jul-2020
PHASE OF DEVELOPMENT: Phase 1/2
BACKGROUND AND RATIONALE FOR THE STUDY: Tinostamustine is a first-in-class alkylating HDACi fusion molecule that is multi-action therapy designed to improve drug access to deoxyribonucleic acid (DNA) strands, induce DNA damage and counteract its repair in cancer cells. *In vitro* and *in vivo* pharmacology studies demonstrated alkylating and HDACi activities of tinostamustine as well as cytotoxic and anti-tumour activities against various solid tumours.
OBJECTIVES: **Phase 1: Dose Escalation until Maximum Administered Dose (MAD):** **Primary objective:** To determine the safety, tolerability, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of tinostamustine as a single agent in subjects with solid tumours who have progressed after at least one (1) line of therapy and no other standard therapy with proven clinical benefit is available. The MTD was determined for two (2) administration schedules: (A) intravenously (i.v.) on Day 1 and Day 15 of each 4-week treatment cycle, and (B) i.v. on Day 1, Day 8 and Day 15 of each 4-week treatment cycle. **Secondary objective:** To establish the pharmacokinetic (PK) profile of tinostamustine **Phase 2: Evaluation of Toxicity and Response Rate in Selected Solid Tumour Cohorts:** **Primary objective:** To determine the objective response rate (ORR) [complete response (CR) plus partial response (PR)] and the clinical benefit rate (CR, PR and stable disease) of the RP2D of the selected schedule at four (4) or six (6) months depending on selected tumour type. **Secondary objectives:** ▪ To evaluate safety and tolerability of the RP2D of the selected schedule of tinostamustine. ▪ To determine the progression free survival time for subjects who received the RP2D at the selected drug administration schedule. ▪ To determine the overall survival time for subjects who received the RP2D at the selected drug administration schedule.

- To determine duration of response.
- To establish the trough PK profiles of tinostamustine.

Exploratory objective:
To correlate the extent of gene expression changes in tumour samples with anti-tumour activity.

METHODOLOGY: This study was a multi-centre, open-label phase 1/2 study of single agent tinostamustine in subjects with advanced solid tumours. Phase 1 part of the study was designed to define the MTD, the PK of tinostamustine and its two metabolites, M2 and M8, in each drug administration schedule (Schedule A: Day 1 and Day 15; Schedule B: Day 1, Day 8, and Day 15) and to identify the RP2D. Phase 2 part of the study was designed to evaluate the ORR and the clinical benefit rate of the RP2D at four (4) or six (6) months depending on the selected tumour type. This report relates to Phase 1 part only as Phase 2 part is ongoing at the time of writing the report.

Subjects were eligible for this study if they had a histologically confirmed solid tumour, signed informed consent and met the inclusion/exclusion criteria. After consenting, subjects were screened, and all procedures were performed as required.

Phase 1: Dose Escalation until MAD
In Phase 1, tinostamustine doses were escalated following the standard 3+3 design[1)]. The decision to escalate to the next dose level occurred after all subjects in the cohort completed Cycle 1 of treatment and were evaluated for safety and toxicity. A Safety Review Committee that included the Investigators and Sponsor/sponsor's representatives reviewed available data including toxicity and activity data to reach consensus on dose levels and determination of the MTD and RP2D.

In the 3+3 design, if one of the three (3) subjects had a dose-limiting toxicities (DLTs), the cohort was expanded to a maximum of six (6) subjects. If only one (1) of the six (6) subjects had a DLT, dose escalation continued. If two (2) subjects had a DLT, dose escalation stopped, regardless of the number of subjects that were treated in this cohort (e.g., if subjects 1 and 4 had DLTs then subjects 5 and 6 would not be treated). If two (2) or more DLTs occurred in a six-subject cohort, this dose was declared the MAD, and the prior dose level or an intermediate dose level was declared the MTD. The MTD was confirmed when six (6) subjects were treated at a dose level with less than two (2) DLTs. In case a subject experienced a DLT at dose level 1 (60 mg/m^2), the study drug was to be reduced one dose level to 40 mg/m^2.

Enrolment to the two (2) dose administration schedules was to be sequential. Subjects were enrolled first into Schedule A. The starting dose in Schedule A was 60 mg/m^2 (dose level 1). Doses were escalated in Schedule A until MAD for this schedule was determined. The starting dose for Schedule B was to be determined after analysing all the safety, toxicity and the PK data from Schedule A; however, the starting dose in Schedule B would not exceed one dose level below the MTD determined in Schedule A. The MTDs for both schedules were to be determined.

Subject assessments, except for imaging tests, were performed at the end of each treatment cycle and at the time of study drug discontinuation (at any time or Day 28 of the last treatment cycle).

To ensure subjects' safety, stopping rules applied. If 66% or more subjects treated at any given time of Phase 1 part experienced the following Grade 2 toxicities, the study was to be stopped for enrolment and the risk would be assessed and addressed by the Sponsor.
- Grade 2 venous thrombosis
- Grade 2 increase of serum creatinine (> 1.5 - 3.0 x upper limit of normal [ULN])
- Grade 2 nervous system disorders excluding headache

The RP2D and administration schedule were defined by the Sponsor after all information on safety, toxicity, and pharmacokinetics of the various dose levels and in respect of the underlying diseases was reviewed. The following data were considered for the selection of the administration schedule and the respective RP2D to go forward to Phase 2 part:
- DLTs and all study drug-related Grade 2 toxicities in all escalation cohorts
- Dose modifying events which were similar to DLTs but occurred subsequent to Cycle 1

- Maximum dose delivered per administration in a schedule and the related maximum plasma concentration (C_{max}) during infusion consistently delivering > 1µM of tinostamustine
- Quality of response and duration of response in all cohorts

NUMBER OF SUBJECTS (planned and analysed):
Phase 1: A maximum of 42 subjects were planned to be enrolled.
The actual number of subjects exposed to tinostamustine was 22.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION:
The main inclusion criteria were as follows:

- Subjects age ≥ 18 years at signing the informed consent.
- Histologically confirmed diagnosis of advanced or metastatic solid tumours, disease should have progressed following at least one line of therapy and no other standard therapy with proven clinical benefit is available.
- Subjects with secondary metastasis to the central nervous system (CNS) are eligible if they have had brain metastases resected or have received radiation therapy ending at least 4 weeks prior to study Day 1 and they meet all of the following criteria:
  (1) Residual neurological symptoms ≤ Grade 1.
  (2) No glucocorticoids requirement or subjects may be receiving low doses of glucocorticoids providing the dose has been stable for at least two weeks prior to starting the study medication.
  (3) Follow-up magnetic resonance imaging shows no progression of treated lesions and no new lesions
- Evaluable disease: either measurable on imaging or with informative tumour marker as assessed by RECIST version 1.1 or other relevant response assessment for tumour type.
- Discontinuation of previous cancer therapies at least three (3) weeks or 5 half-lives, whichever is shorter, as long as the subject has recovered to eligibility levels prior to treatment in this study.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
- Neutrophils ≥ 1,500/µL.
- Platelets ≥ 100,000/µL.
- Aspartate aminotransferase (AST) / alanine aminotransferase (ALT) ≤ 3 x ULN. In cases with liver involvement, ALT/AST ≤ 5 x ULN.
- Total bilirubin < 1.5 mg/dL unless elevated due to known Gilbert's syndrome.
- Creatinine ≤ 1.5 x ULN.
- Serum potassium within normal range.

The main exclusion criteria were as follows:

- Subjects with primary CNS cancer.
- Subjects with corrected QT interval (QTc) using Fridericia's formula > 450 msec in male and > 470 msec in female.
- Subjects who are on treatment with drugs known to prolong the QT/QTc interval.
- Subjects who are being treated with Valproic Acid for any of its indication (epilepsy, mood disorder) must be excluded or must stop using the medication and have a wash out period of 3.3 days prior to first dose of study drug treatment in this study.
- Any serious medical condition that interferes with adherence to study procedures.
- Prior history of solid tumour malignancy diagnosed within the last three (3) years of study enrolment excluding adequately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or *in situ* cervical cancer, *in situ* breast cancer, *in situ* prostate cancer (subjects must have shown no evidence of active disease for two (2) years prior to enrolment).
- Use of other investigational agents within 30 days or 5 half-lives prior to the first dose of study drug. As long as subject has recovered from any related toxicities ≥ Grade 1.
- Steroid treatment within seven (7) days prior to study treatment. Subjects that require intermittent use of bronchodilators, topical steroids or local steroid injections will not be excluded from the study. Subjects who have been stabilized to 10 mg Prednisolone PO QD (or equivalent) daily (or less) at least seven (7) days prior to study drug administration are allowed.

Company name: Mundipharma Research Limited **Study number: EDO-S101-1002**
Test product: Tinostamustine (EDO-S101) **CSR Version 1, 16 December 2022**

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NUMBER(S):
Tinostamustine was provided as a lyophilized powder in single dose, sealed glass vials. Each 50 mL vial contained 100 mg tinostamustine.
Tinostamustine was administered on Day 1 and Day 15 of each 4-week treatment cycle in Schedule A by i.v. infusion through a peripheral vein or central catheter over the specified infusion time. The dose levels and infusion times in Phase 1 part are defined in Section 9.4.1.1.
Batch number used in Phase 1 part: 1706001

DURATION OF TREATMENT: While subjects were expected to receive a median of four (4) cycles of therapy, the maximum number of treatment cycles planned was six (6). At the Investigators' discretion, responding subjects or subjects who experienced clinical benefit were allowed to continue the treatment beyond six (6) cycles. The treatment was continued until disease progression or intolerable toxicity.

CONTROL PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NUMBER(S): not applicable

ENDPOINTS:

Safety (include those measures taken to protect subjects):
The MTD was defined by assessing safety, DLTs and toxicity during dose escalation.
Other safety assessments included physical examinations, ECOG performance status, electrocardiograms (ECGs), pregnancy testing for women of childbearing potential, treatment-emergent adverse events (TEAEs), clinical laboratory evaluations including haematology, blood chemistry and urinalysis, vital signs, and concomitant medication usage.

Efficacy:
Radiologic response assessment by computed tomography (CT) scans or positron emission tomography (PET)/CT was performed at baseline and every two (2) cycles. Tumour response was evaluated according to the response evaluation criteria in solid tumours (RECIST) version 1.1[2)] (defined in Appendix C of the protocol).

Pharmacokinetics:
Plasma samples were collected to determine the concentrations of tinostamustine, and its two metabolites M2 and M8, by a method fully validated according to the relevant guidelines. The PK profiles of tinostamustine in plasma were assessed in each subject. The blood sampling was taken in Cycle 1 only at each drug administration.
The blood sampling schedule was as follows: 0.5 hour (+/- 10 minutes) prior to dose administration, and at 15, 30, 45 minutes and 1 hour (+/-5 minutes), 1.5, 2, 3, 6 hours (+/- 10 minutes), 24 hours (+/- 2 hours) from the start of tinostamustine infusion.

Pharmacodynamics:
For exploratory purposes, the pharmacodynamics evaluations were planned to be performed.
Subject participation in the gene expression analysis was not required for enrolment into the study. If the subject agreed to participate in the gene expression analysis, a fresh or archival tissue sample was collected during Screening. Formalin fixed paraffin embedded biopsy samples were used.
The expression profile was to be analysed for correlation with response or resistance to therapy. Results of the gene expression analysis are not included in this report and will be described in a separate report when the analysis is completed.

STATISTICAL METHODS:
The statistical analyses were briefly described in the protocol and more details are contained in the statistical analysis plan.

Study Populations

- **Full Analysis Population**

All subjects who received at least one dose of study treatment were included in the Full Analysis Population. Efficacy analyses were performed on data from all subjects in the Full Analysis Population.

- **Safety Population**

All subjects who received at least one dose of study treatment were included in the Safety Population. Safety analyses were performed on data from all subjects in the Safety Population.

- **PK Population**

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

Data Analysis

- **Demographics and Baseline Characteristics**

Demographic information included age, sex, ethnicity, and race. Demographics and baseline characteristics were summarised descriptively. Height and weight were reported with the demographic information listed above. Subject demographics (sex, ethnicity, race, and age category) were presented using discrete summary statistics. Age, height, and weight were presented using continuous summary statistics.

- **Safety Analysis**

The safety analysis summarised TEAEs for all treated subjects using discrete summaries at the subject- and event-level by system organ class and preferred term. Treatment-related TEAEs, TEAEs leading to death, SAEs, and TEAEs resulting in study discontinuation were summarised similarly. TEAEs were also summarised by the grade of National Cancer Institute Common Terminology Criteria for Adverse Events.

ECOG status was summarised at Screening and at study drug discontinuation.

Results of laboratory tests, including haematology, chemistry, and urinalysis were summarised by treatment cycle (and day) and for change from baseline to the treatment cycle (and day) using continuous summary statistics (mean, standard deviation [SD], minimum, median, and maximum).

Vital signs were summarised using continuous summary statistics (mean, SD, minimum, median, and maximum) by treatment cycle and day, including change from baseline summaries and worst-case summaries.

ECG measures were summarised using continuous summary statistics (mean, SD, minimum, median, and maximum) by treatment cycle, including change from baseline summaries and worst-case summaries.

Study drug exposure was summarised using continuous summary statistics on the total drug exposure and total days of exposure as well as discrete summary statistics on the number of treatment cycles of exposure.

- **Efficacy Analysis**

Overall response at subsequent assessments and last follow-up status were summarised under the dose cohort in which subjects were enrolled.

- **PK Analysis**

PK parameters at all doses included C_{max}, area under the curve (AUC) from 0 time to the last measurable concentration, AUC from 0 time extrapolated to infinity, time to C_{max} (t_{max}), apparent elimination half-life ($t_{1/2}$), total body clearance (CL), apparent volume of distribution based on the terminal phase (V_z), and terminal phase rate constant (λ_z). Other PK parameters were to be calculated, as appropriate.

SUMMARY OF RESULTS AND CONCLUSIONS:

Subject Disposition:

- In Phase 1 part, a total of 26 subjects were screened. Of these subjects, 22 subjects were treated with tinostamustine.
- All treated subjects were included in Safety Population (n = 22, 100.0%). In addition, all 22 subjects of Safety Population were included in PK Population.
- All treated subjects completed Cycle 1 (n = 22, 100.0%), and 11 subjects (50.0%) completed Phase 1. Other 11 subjects (50.0%) discontinued the study due to PD (n = 5, 45.5%), death (n = 3, 27.3%), TEAE, patient's decision and Investigator's decision (n = 1, 9.1%, for each).

Demography and Baseline Characteristics:

- In all 22 treated subjects, there were 9 males (40.9%) and 13 females (59.1%) treated, with a median age of 62.0 years (range 35-74). Most of the subjects were White (n = 17, 77.3%).
- The cancer diagnoses at baseline included ovarian cancer (3 subjects), breast cancer, non-small cell lung cancer (each 2 subject), adenocarcinoma of colon, adenoid cystic carcinoma, adrenal gland cancer, cervix cancer, endometrial cancer, leiomyosarcoma, lung cancer, nasopharyngeal cancer, pancreatic carcinoma, papillary thyroid cancer, pleomorphic adenoma, rectal cancer, renal cell carcinoma, tonsil cancer, uterine cancer (each 1 subject).

Efficacy Results:

- Of all 22 treated subjects, one subject had PR, 11 subjects had stable disease and 7 subjects had PD.
- Of all 22 treated subjects, 3 subjects (13.6%) were alive and 17 subjects (77.3%) were dead at last survival follow-up, one subject (4.5%) was lost to follow-up, and one subject (4.5%) had no survival follow-up performed.

PK Results:

- The mean of C_{max} and AUCs generally increased with increasing dose over the range of 60 -100 mg/m^2 with each infusion duration of 30 and 60 minutes. When equivalent dose levels of tinostamustine were compared, the mean C_{max} for the 30-minute infusion was approximately 1.5- to 3-fold higher than that for the 60-minute infusion. Generally, T_{max} occurred prior to or at the end of the tinostamustine infusion. There was no marked accumulation of exposure on Day 15 following repeated dosing when compared to Day 1 for either C_{max} or AUC.
- In regard to the metabolites (M2 and M8), the plasma concentrations of M2 and M8 were much lower than those of tinostamustine. Over the dose range the M2 plasma concentrations appeared lower than those observed for M8. The ratio of each metabolite to tinostamustine was considered small and showed some variability. However no clear trends in the ratios were observed with increasing dose levels or study day or infusion duration. The relationship between dose and exposure to these metabolites was similar to that observed for tinostamustine.

Safety Results:

- All 22 subjects (100.0%) experienced at least one TEAE, and at least one treatment-related TEAE. Fifteen subjects (68.2%) experienced at least one serious TEAE, and one subject (4.5%) experienced at least one TEAE leading to death. Nine subjects (40.9%) experienced at least one TEAE resulting in permanent withdrawal of study drug, 15 subjects (68.2%) experienced at least one TEAE leading to dose reduction, interruption or discontinuation.
- All 22 subjects experienced ≥ Grade 2 TEAEs. Twelve subjects (54.5%) experienced Grade 3 events, 6 subjects (27.3%) experienced Grade 4 events, and one subject (4.5%) experienced Grade 5 events as the worst grade per subject.
- In the 30-minute infusion cohorts of Schedule A (administered on Day 1 and Day 15 of each 4-week treatment cycle), study drug dosing had to be delayed in subsequent cycles due to thrombocytopenia, which was associated with an extremely high C_{max} of tinostamustine. To ensure that subjects continue the study treatment safely, the Sponsor decided to stop the investigation of the 30-minute infusion time and open the 60-minute infusion cohort.
- In the cohort of 100 mg/m^2 given over 60 minutes, one of two treated subjects experienced Grade 3 electrocardiogram QT prolonged, which was reported as a DLT. Considering the DLT observed in this cohort and the rapid occurrence of treatment-induced thrombocytopenia (not meeting the DLT definitions), the SRC concluded as follows:
  - The dose level of 100 mg/m^2 given i.v. over 60 minutes was determined to be the MAD for Schedule A
  - The dose level of 80 mg/m^2 given i.v. over 60 minutes was determined to be the MTD for Schedule A
  - There was no need to further investigate Schedule B (administered on Day 1, Day 8 and Day 15 of each 4-week treatment cycle)
  - The dose level of 80 mg/m^2 given i.v. over 60 minutes on Day 1 and Day 15 of each 4-week treatment cycle was determined to be the RP2D

- TEAEs occurring in ≥ 30% of subjects were nausea (n = 19, 86.4%), anaemia (n = 15, 68.2%), electrocardiogram QT prolonged, fatigue, and platelet count decreased (n = 14, 63.6%, for each), vomiting (n = 12, 54.5%), lymphocyte count decreased (n = 10, 45.5%), decreased appetite (n = 8, 36.4%), headache, hypokalaemia, and white blood cell count decreased (n = 7, 31.8%, for each).
- Treatment-related TEAEs occurring in ≥ 30% of subjects were nausea (n = 18, 81.8%), electrocardiogram QT prolonged and platelet count decreased (n = 14, 63.6%, for each), anaemia (n = 12, 54.5%), fatigue (n = 11, 50.0%), lymphocyte count decreased (n = 10, 45.5%), vomiting (n = 9, 40.9%), and white blood cell count decreased (n = 7, 31.8%).
- Grade 3 TEAEs occurring in > 1 subject were anaemia (n = 6, 27.3%), lymphocyte count decreased (n = 4, 18.2%), electrocardiogram QT prolonged, neutrophil count decreased, and platelet count decreased (n = 3, 13.6%, for each), small intestinal obstruction and acute kidney injury (n = 2, 9.1%, for each). Grade 4 TEAEs were lymphocyte count decreased (n = 5, 22.7%) and platelet count decreased (n = 1, 4.5%).
- One subject experienced TEAEs leading to death, those were intestinal perforation and septic shock (4.5% for each) considered unrelated to study drug.
- Serious TEAEs occurring in > 1 subjects were lymphocyte count decreased (n = 6, 27.3%), electrocardiogram QT prolonged, platelet count decreased, and small intestinal obstruction (n = 3, 13.6%, for each), and acute kidney injury (n = 2, 9.1%).
- TEAEs resulting in permanent withdrawal of study drug occurring in > 1 subjects were anaemia, gamma-glutamyltransferase increased, and platelet count decreased (n = 3, 13.6%, for each), hypomagnesaemia, neutrophil count decreased, urinary tract infection, and white blood cell count decreased (n = 2, 9.1%, for each).
- TEAEs leading to dose reduction, interruption or discontinuation occurring in > 1 subjects were platelet count decreased (n = 10, 45.5%), anaemia and neutrophil count decreased (n = 5, 22.7%, for each), gamma-glutamyltransferase increased and white blood cell count decreased (n = 3, 13.6%, for each), fatigue, hypokalaemia, hypomagnesaemia, lymphocyte count decreased, and urinary tract infection (n = 2, 9.1%, for each).
- All 12-lead ECGs were performed using ECG machines each study site had and evaluated by a reviewer at each study site (local ECGs). Of all 22 treated subjects, 14 subjects (63.6%) experienced at least one event of electrocardiogram QT prolonged, which were observed across all dosing cohorts except the cohort of 60 mg/m2 given over 60 minutes. The NCI CTCAE grades of these events were mostly Grade 1. Grade 2 events occurred in 4 subjects, and Grade 3 events occurred in 3 subjects. All Grade 3 events were SAEs, and one of them led to dose reduction. There was no event leading to dose discontinuation. In most cases, the events were resolved without any action taken with study drug or other medication.
- The local ECGs that showed Grade 2 or Grade 3 electrocardiogram QT prolonged were retrospectively evaluated by an independent cardiologist for central review. The results were as follows: two subjects had QTcF increase > 60 ms in the cohort of 80 mg/m^2 given over 30 minutes, one subject had QTcF increase > 60 ms in the cohort of 100 mg/m^2 given over 30 minutes, and one subject had QTcF > 500 ms in the cohort of 100 mg/m^2 given over 60 minutes.

Conclusions:
Overall, in Phase 1 of the study, tinostamustine had an acceptable safety profile in subjects with advanced solid tumour. PK exposure parameters generally increased with increasing dose over the range of 60-100 mg/m^2 with each infusion duration of 30 and 60 minutes. The shorter infusion duration resulted in a higher C_{max}. There was no marked accumulation of exposure following repeated dosing.
The dosing schedule of 80 mg/m^2 given i.v. over 60 minutes on Day 1 and Day 15 of each 4-week treatment cycle was determined to be the RP2D.
In the ongoing Phase 2 of the study, the efficacy and safety of the RP2D will be further evaluated.

DATE AND VERSION OF THIS REPORT: Version 1, 16 December 2022