Company name: Mundipharma Research Limited **Study number: EDO-S101-1002**
Test product: Tinostamustine (EDO-S101) **CSR Version 1, 18 December 2023**

1. TITLE PAGE

CLINICAL STUDY REPORT

Note: This report only presents the data from Phase 2 part and 2 sub-studies shown below. Phase 1 part was reported separately.

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,

SUB-STUDY TO CHARACTERIZE THE EFFECTS OF TINOSTAMUSTINE AT A DOSE OF 60 MG/M^2 ADMINISTERED DURING A 60-MINUTE INFUSION ON CARDIAC REPOLARIZATION IN PATIENTS WITH ADVANCED SOLID TUMORS,

SUB-STUDY TO CHARACTERIZE THE EFFECTS OF TINOSTAMUSTINE AT A DOSE OF 80 MG/M^2 ADMINISTERED DURING A 80-MINUTE INFUSION ON CARDIAC REPOLARIZATION 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

Signature: DocuSigned by: Kasia Hilgier
Signer Name: Kasia Hilgier
Signing Reason: I approve this document
Signing Time: 19 December 2023 | 12:16:56 PM GMT
5C544089EF9146908B50098C8EC448DC

Date (dd-mmm-yyyy)

Nick Manamley, MSc.
Head of Biometrics

Signature: DocuSigned by: Nick Manamley
Signer Name: Nick Manamley
Signing Reason: I approve this document
Signing Time: 19 December 2023 | 1:57:46 PM GMT
DBBEEF7576A44159BB304596C2F3A049

Date (dd-mmm-yyyy)

Protocol Number: EDO-S101-1002
Trial Registry name and number: ClinicalTrials.gov NCT03345485
IND Number: 125180
EudraCT Number: 2020-004246-11
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.

Company name: Mundipharma Research Limited **Study number: EDO-S101-1002**
Test product: Tinostamustine (EDO-S101) **CSR Version 1, 18 December 2023**

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
- Sub-study to Characterize the Effects of Tinostamustine at a Dose of 60 mg/m^2 Administered during a 60-minute Infusion on Cardiac Repolarization in Patients with Advanced Solid Tumors
- Sub-study to Characterize the Effects of Tinostamustine at a Dose of 80 mg/m^2 Administered during an 80-minute Infusion on Cardiac Repolarization in Patients with Advanced Solid Tumors

PROTOCOL NUMBER: EDO-S101-1002, EDO-S101-1002 sub study

PRINCIPAL INVESTIGATOR NAME:
(Until 11-July-2021)
Shivaani Kummar, MD, FACP. Oregon Health & Science University, Portland, Oregon, United States
(After 12-July-2021)
Ana Oaknin, MD, PhD. Hospital Universitari Vall d'Hebron, Barcelona, Spain

NUMBER OF STUDY CENTRES AND COUNTRIES (PHASE 2 AND SUB-STUDIES):
4 centres in the United States (US), 3 centres in Canada, 2 centres in Italy, 2 centres in Spain, and 1 centre in the Netherlands (NL)

PUBLICATION (REFERENCES): Tinker A, et al. American Society of Clinical Oncology (ASCO) Annual Meeting 2023. 2-6 June 2023. Chicago, USA. Poster #3021

STUDY PERIOD (PHASE 2 AND SUB-STUDIES):
Date of First Subject First Dose: 26-Dec-2018
Date of Last Subject Last Follow-up: 29-Mar-2023

REPORTING PERIOD (PHASE 2 AND SUB-STUDIES):
Date of First Data Collection: 28-Nov-2018
Date of Last Data Collection: 29-Mar-2023

PHASE OF DEVELOPMENT: Phase 1/2

BACKGROUND AND RATIONALE FOR THE STUDY: Tinostamustine is a first-in-class alkylating HDACi 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 1 line of therapy and for whom no other standard therapy with proven clinical benefit is available. The MTD was determined for intravenous (i.v.) administration on Day 1 and Day 15 of a 4-week treatment cycle.

Secondary objective:

To establish the pharmacokinetic (PK) profile of tinostamustine

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

Primary objective:

To determine the objective response rate (ORR) (complete response [CR] plus partial response [PR]) of any duration, plus the rate of subjects with stable disease (SD) of at least 12-week duration at a dose of 80 mg/m^2 administered over 1 hour on Day 1 and Day 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 Day 15 of each 4-week treatment cycle.
- To determine the progression free survival (PFS) time for subjects who received 80 mg/m^2 of tinostamustine administered over 1 hour on Day 1 and Day 15 of each 4-week treatment cycle.
- To determine the overall survival (OS) time for subjects who received 80 mg/m^2 of tinostamustine administered over 1 hour on Day 1 and Day 15 of each 4-week treatment cycle.
- To determine duration of response (DoR).
- To establish the whole PK profiles of tinostamustine.

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

Sub-study 1: Dose of 60 mg/m^2 Administered during a 60-minute Infusion
Primary objective:
To characterize the effect of tinostamustine at a dose of 60 mg/m^2 on cardiac repolarization (QTcF: corrected QT interval [QTc] using Fridericia's formula) and other electrocardiogram (ECG) parameters in 6 subjects with solid tumours who have progressed after at least 1 line of therapy and for whom no other standard therapy with proven clinical benefit is available. Tinostamustine was to be administered intravenously on Day 1 and Day 15 of each 4-week treatment cycle.

Secondary objectives:
- To evaluate safety and tolerability of tinostamustine
- To establish the PK profile of tinostamustine 60 mg/m^2 administered over 1 hour on Day 1 and Day 15 of each 4-week treatment cycle.
- To determine ORR, the clinical benefit rate (CBR [CR, PR plus SD]), and SD of at least 12-week duration
- To determine PFS
- To determine OS
- To determine DoR

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

Sub-study 2: Dose of 80 mg/m^2 Administered during an 80-minute Infusion
Primary objective:
To characterize the effect of tinostamustine at a dose of 80 mg/m^2 on cardiac repolarization (QTcF) and other ECG parameters in 6-12 subjects with solid tumours who have progressed after at least 1 line of therapy and for whom no other standard therapy with proven clinical benefit is available. Tinostamustine was to be administered intravenously on Day 1 and Day 15 of each 4-week treatment cycle.

Secondary objectives:
- To evaluate safety and tolerability of tinostamustine
- To determine the plasma concentrations of tinostamustine and its metabolites (M2 and M8) following tinostamustine administration of 80 mg/m^2 over 80 minutes on Day 1 and Day 15 of a 4-week treatment cycle.
- To determine ORR, CBR, and SD of at least 12-week duration
- To determine PFS
- To determine OS
- To determine DoR

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, and to identify the RP2D. In October 2018, the Safety Review Committee (SRC) recommended 80 mg/m^2 administered over 1 hour on Day 1 and Day 15 of each 4-week treatment cycle as the dose for Phase 2. The results of Phase 1 part have been reported separately.

Phase 2 part of the study was designed to evaluate the ORR of the RP2D (80 mg/m^2 of tinostamustine administered over 1 hour on Day 1 and Day 15 of each 4-week treatment cycle) at 4 or 6 months, depending on the type of solid tumour. Secondary objectives were evaluation of safety and tolerability of the RP2D in selected solid tumours.

In addition, sub-studies were designed to better characterize the effect of tinostamustine at 60 mg/m^2 administered over 60 minutes or 80 mg/m^2 administered over 80 minutes on cardiac repolarization (QTc) and other ECG parameters in the subjects with solid tumours being investigated in the phase 1/2 study.

Subjects were eligible for these studies 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 per protocol.

This report relates to Phase 2 and two sub-studies, only.

Phase 2: Evaluation of Response Rate in Selected Solid Tumour Cohorts
In Phase 2, five cohorts were opened to recruit subjects with:
(1) relapsed/refractory small cell lung cancer (SCLC)
(2) relapsed/refractory soft tissue sarcoma (STS)
(3) relapsed/refractory triple-negative breast cancer (TNBC)
(4) relapsed/refractory ovarian cancer
(5) relapsed/refractory endometrial cancer

Each cohort was to recruit 10 subjects who would be treated at 80 mg/m^2 administered over 1 hour on Day 1 and Day 15 of each 4-week treatment cycle and monitored for safety and efficacy. Each cohort could treat additional 19 subjects (29 in total) if there was evidence of 2 successes in that cohort. Success was defined as either CR or PR of any duration, or SD of at least 12-week duration. The Sponsor could suspend or discontinue enrolment to the cohorts at any time due to slow subject accrual rates or other reasonable cause.

On 05 March 2021, following an evaluation of the development of tinostamustine across multiple studies, the Sponsor took the decision to halt recruitment into the cohorts for relapsed/refractory TNBC and relapsed/refractory endometrial cancer on this study. This decision was made to enable focusing of resources on the other 3 cohorts.

Treatment could be continued until progression or intolerable toxicity, up to a maximum of 12 treatment cycles. The Investigator and the Sponsor could decide to reduce a subject's dose to 60 mg/m^2 in case of toxicity leading to dose delays. If toxicity issues were resolved, the original dose could be administered at the next cycle. If the subject did not tolerate the reduced dose, then the subject was withdrawn from the study.

Subject assessments, except for imaging tests, were performed at the end of each treatment cycle and at the time of Investigational Medicinal Product (IMP) discontinuation (at any time or Day 28 of the last treatment cycle). Tumour response assessment by imaging was performed according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1[1)] (defined in Appendix C of the protocol) at baseline, every 2 treatment cycles, and every 2 months after treatment discontinuation until documentation of progressive disease (PD) or the initiation of a subsequent anti-cancer therapy, whichever came first.

The PK profiles of tinostamustine and its metabolites (M2 and M8) were to be assessed in Cycle 1 in a minimum of 50 subjects.

Since QTc prolongations were defined as events of special interest the following stopping rules were developed for subjects who experienced QTc prolongations >500 msec or change from baseline >60 msec (Grade 3) that were not transient or occurred in more than 1 treatment cycle.
If the QTcF value on the ECG machine printout was >500 msec or represented an increase of >60 msec from baseline, 2 additional ECGs were to be performed approximately 1 minute apart. If the average QTcF of the 3 ECGs was >500 msec or increased >60 msec from baseline, the tinostamustine infusion had to be stopped. The subject had to stay in the unit until the QTcF

decreased to baseline. In addition, the subject was to be continuously observed for syncope or other clinically relevant cardiac events.

A thorough evaluation of ECGs, including the expedited central review of Grade 3 QTc prolongations by an independent assessor, needed to be performed. The decision would be made by the Investigator in consultation with the Medical Monitor, whether study treatment should continue, be postponed, or be stopped.

Sub-study 1: Dose of 60 mg/m^2 Administered during a 60-minute Infusion
A subgroup of 6 subjects treated with a dose of 60 mg/m^2 tinostamustine administered over 60 minutes was studied with intense ECG measurements, including 24-hour Holter monitoring, and PK sampling. The PK sampling was performed on Day 1 and Day 15 in Cycle 1. If Grade 3 or higher QTcF prolongation (defined in National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) or QTcF increased > 60 msec from baseline occurred in any 2 or more subjects or a fatal cardiac event related to tinostamustine occurred in 1 or more subjects, the study would be stopped.
The relationship with maximum plasma concentration (C_{max}) was to be examined relative to any prolongation of QTcF seen on central ECG reading and simple descriptive statistics were to be applied as appropriate.
Following enrolment of 6 subjects the study was to be stopped. Additionally, if any 2 or more subjects had Grade 3 or higher centrally confirmed QTc prolongation or QTcF increased >60 msec from baseline or 1 or more subject had a fatal cardiac event related to tinostamustine, this sub-study was to be stopped.

Sub-study 2: Dose of 80 mg/m^2 Administered during an 80-minute Infusion
A subgroup of 6 to 12 subjects treated with a dose of 80 mg/m^2 tinostamustine administered over 80 minutes was studied with intense ECG measurements, including 30-hour Holter monitoring, and PK sampling performed on Day 1 and Day 15 in Cycle 1.
The relationship with C_{max} was to be examined relative to any prolongation of QTcF seen on central ECG reading and simple descriptive statistics were to be applied as appropriate.
Following enrolment of 6-12 subjects, this sub-study was to be stopped.

NUMBER OF SUBJECTS (PLANNED AND ANALYSED):
Phase 2:
- Number of subjects planned to be enrolled: 56 to 160 subjects (10 or 29 evaluable subjects in each cohort)
- Number of subjects exposed to tinostamustine: 36 subjects

Sub-study 1:
- Number of subjects planned to be enrolled: 6 subjects at a maximum
- Number of subjects exposed to tinostamustine: 6 subjects

Sub-study 2:
- Number of subjects planned to be enrolled: 12 subjects at a maximum
- Number of subjects exposed to tinostamustine: 7 subjects

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION:
In Phase 2, 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 during or following at least 1 previous line of therapy and no other standard therapy with proven clinical benefit was available or recommended based on the Investigator's individual risk-benefit assessment for the subject.
- Subjects with secondary metastasis to the central nervous system (CNS) were eligible if they had brain metastases resected or had received radiation therapy ending at least 4 weeks prior to study Day 1 and they met all of the following criteria:
  (1) Residual neurological symptoms ≤ Grade 1.
  (2) No glucocorticoids requirement or subjects receiving low doses of glucocorticoids providing the dose had been stable for at least 2 weeks prior to starting the study medication.
  (3) Follow-up imaging tests showed no progression of treated lesions and no new lesions

- Evaluable disease: measurable on imaging as assessed by RECIST version 1.1.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
- Absolute neutrophil count (ANC) (polymorphonuclear [PMN] cells plus bands) >1,000 /µL.
- Platelets ≥100,000 /µL. Platelet transfusions within the 14 days before Day 1 of Cycle 1 was prohibited.
- Aspartate aminotransferase (AST) / alanine aminotransferase (ALT) ≤3 x upper limit of normal (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 and magnesium at least at the lower limit of normal (LLN) before every IMP administration. If it was below LLN, supplementation was permissible.

In Phase 2, the main exclusion criteria were as follows:

- Subjects with primary CNS cancer.
- Subjects with QTcF >450 msec.
- Subjects who were on treatment with drugs known to prolong the QT/QTc interval. Refer to CredibleMeds list of drugs with known risk of Torsade de pointe (TdP): http://crediblemeds.org/new-drug-list.
- Subjects who were being treated with Valproic Acid for any indication (epilepsy, mood disorder).
- Any serious medical condition that interfered with adherence to study procedures.
- Prior history of another solid tumour malignancy diagnosed within the last 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 2 years prior to enrolment).
- Use of other investigational agents or previous anticancer therapies within 28 days prior to the first dose of tinostamustine, provided the subject has recovered from any related toxicities ≥ Grade 1.
- Steroid treatment within 7 days prior to study treatment. Subjects that required intermittent use of bronchodilators, topical steroids or local steroid injections would not be excluded from the study. Subjects who had been stabilized to 10 mg prednisolone orally (PO) once daily (QD) (or equivalent) daily (or less) at least 7 days prior to tinostamustine administration were allowed.

In addition, the cohort-specific inclusion/exclusion criteria in Phase 2 were as follows:

Cohort 1: Relapsed/Refractory SCLC

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

Cohort 2: Relapsed/Refractory STS

1. Histologically confirmed diagnosis of advanced, unresectable, or metastatic STS not amenable to curative treatment with surgery or radiotherapy, excluding neuroblastoma, gastrointestinal stromal tumours (GIST), embryonal rhabdomyosarcoma, Kaposi sarcoma, chondrosarcoma, osteosarcoma or Ewing's sarcoma.
2. Must have received at least 1 prior line chemotherapy or biological therapy regimen and no other standard therapy with proven clinical benefit was available or recommended based on the Investigator's individual risk-benefit assessment for the subject. At least 28 days should have

elapsed since prior chemotherapy as long as the subject recovered from any related toxicities to ≤ Grade 1 (or ≤ Grade 2 for any symptomatic neuropathy or endocrinopathies).
3. The disease had to be progressing during or relapsing after the previous treatment.
4. Presence of measurable disease as defined by RECIST version 1.1. Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, were usually not considered measurable unless there had been demonstrated progression in the lesion.

Cohort 3: Relapsed/Refractory TNBC

1. Histologically or cytologically confirmed locally advanced or metastatic TNBC. Proven human epidermal growth factor receptor 2 (HER2) negative by immunohistochemistry or *in situ* hybridization per American Society of Clinical Oncology - College of American Pathologists (ASCO-CAP) guidelines (defined in Appendix D of the protocol).
2. Must have received at least 1 line of chemotherapy or biological therapy and no other standard therapy with proven clinical benefit was available or recommended based on the Investigator's individual risk-benefit assessment for the subject.
3. At least 3 weeks should have elapsed since prior chemotherapy as long as the subject recovered from acute toxicity of previous therapies to ≤ Grade 1 (or ≤ Grade 2 for any symptomatic neuropathy or endocrinopathies).
4. Prior radiotherapy was acceptable provided it was administered at least 4 weeks (2 weeks for palliative, limited field radiation therapy) prior to starting treatment on this study and the subject recovered from any radiotherapy related acute toxicities.
5. The disease had to be progressing during or relapsing after the previous treatment.
6. Presence of measurable disease as defined by RECIST version 1.1. Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, were usually not considered measurable unless there had been demonstrated progression in the lesion.

Cohort 4: Relapsed/Refractory Ovarian Cancer

1. Histologically or cytologically confirmed advanced ovarian cancer epithelial ovarian cancer including primary peritoneal cancer or fallopian tube cancer (excluding borderline ovarian cancer, malignant mixed Mullerian tumour [MMMT]) of high-grade serous histology, or high-grade endometrioid cancer, that was resistant or refractory to platinum therapy and no other standard therapy with proven clinical benefit was available or recommended based on the Investigator's individual risk-benefit assessment for the subject. Clear cell carcinomas were excluded.
   Subjects with primary platinum refractory disease (failure to respond to initial platinum treatment or relapse within 4 weeks) and subjects with primary platinum resistant disease (progression within 6 months of completing first line platinum-based therapy) were excluded from the study.
2. At least 28 days should have elapsed since prior chemotherapy, as long as the subject recovered from acute toxicity of previous therapies to ≤ Grade 1 (or ≤ Grade 2 for any symptomatic neuropathy or endocrinopathies).
3. The disease had to be progressing during or relapsing after the previous treatment.
4. Presence of measurable disease as defined by RECIST version 1.1. Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, were usually not considered measurable unless there had been demonstrated progression in the lesion.

Cohort 5: Relapsed/Refractory Endometrial Cancer

1. Histologically or cytologically confirmed locally advanced or metastatic endometrial cancer (excluding leiomyosarcoma and carcinosarcoma)
2. Must have received at least 1 line of chemotherapy or biological therapy and no other standard therapy with proven clinical benefit was available or recommended based on the Investigator's individual risk-benefit assessment for the subject.
3. At least 3 weeks should have elapsed since prior chemotherapy as long as the subject recovered from acute toxicity of previous therapies to ≤ Grade 1 (or ≤ Grade 2 for any symptomatic neuropathy or endocrinopathies).
4. Prior radiotherapy was acceptable provided it was administered at least 4 weeks (2 weeks for palliative, limited field radiation therapy) prior to starting treatment on this study and recovered from any radiotherapy related acute toxicities.

5. The disease had to be progressing during or relapsing after the previous treatment.
6. Presence of measurable disease as defined by RECIST version 1.1. Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, were usually not considered measurable unless there had been demonstrated progression in the lesion.

The inclusion/exclusion criteria in the sub-studies are described in Section 9.3.2 and 9.3.3.

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.

Phase 2:
Tinostamustine 80 mg/m^2 was administered on Day 1 and Day 15 of each 4-week treatment cycle by i.v. infusion through a peripheral vein or central catheter over 1 hour.

Sub-studies:
Tinostamustine 60 mg/m^2 (in Sub-study 1) or 80 mg/m^2 (in Sub-study 2) was administered on Day 1 and Day 15 of each 4-week treatment cycle by i.v. infusion through a peripheral vein or central catheter over 60 minutes (in Sub-study 1) or 80 minutes (in Sub-study 2).

Batch number used in Phase 2 and 2 sub-studies:
1706001B/C/Q, 1810001A/C/I, 2011001E/F/G.

DURATION OF TREATMENT:

Phase 2:
Tinostamustine could be continued until progression or intolerable toxicity, up to a maximum of 12 treatment cycles.

Sub-studies:
Tinostamustine could be continued up to a maximum of 6 treatment cycles. At the Investigators' discretion and the Sponsor's approval, tinostamustine could be continued beyond 6 treatment cycles in responding subjects or subjects who experienced clinical benefit, up to a maximum of 12 treatment cycles.

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

ENDPOINTS:

Safety (include those measures taken to protect subjects):
Safety assessments included physical examinations, ECOG performance status, 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.

Toxicities were assessed for severity using NCI CTCAE version 4.03, June 2010, with the exception that assessment of QTc prolongations constituting adverse events (AEs) of special interest were based on NCI CTCAE version 5.0, November 2017.

Efficacy:
Efficacy evaluations included ORR, rate of subjects with SD of at least 12-week duration, DoR, PFS, and OS.

Radiologic response assessment by computed tomography (CT) scans or magnetic resonance imaging (MRI) was performed at baseline, every 2 treatment cycles, and every 2 months after treatment discontinuation. Tumour response was evaluated according to the RECIST version 1.1.

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 blood sampling was performed in Cycle 1 at each drug administration on Day 1 and Day 15.

Phase 2:
A minimum of 50 subjects were to be assessed. The blood sampling schedule was as follows: up to 0.5 hour prior to dose administration, at 15, 30, 45 minutes (+/-5 minutes), 1 hour (- 5 minutes but as

close to the calculated end of tinostamustine infusion as possible and before the end of tinostamustine infusion), 75, 90 minutes (+/-5 minutes), 2, 3, 6 hours (+/- 10 minutes), and 24 hours (+/- 2 hours) from the start of tinostamustine infusion.

Sub-study 1:
Each subject was to be assessed. Blood samples were to be collected from the arm opposite of that used for tinostamustine administration, following the 10-minute supine resting periods described for the continuous Holter recordings. The blood sampling schedule was as follows: up to 0.5 hour prior to dose administration, at 15, 30, 45 minutes, 1 hour, 75, 90 minutes (+/-5 minutes), 2, 3, 6 hours (+/- 10 minutes), and 24 hours (+/- 2 hours) from the start of tinostamustine infusion.

Sub-study 2:
Each subject was to be assessed. Blood samples were to be collected from the arm opposite of that used for tinostamustine administration, following the 10-minute supine resting periods described for the continuous Holter recordings. The blood sampling schedule was as follows: within 0.5 hour prior to dose administration, at 5, 10, 20, 30, 45, 60, 80 minutes (+/- 2 minutes), 95, 110, 150 minutes, 3.5, 5, 7, 10 hours (+/- 5 minutes), 24, and 30 hours (+/- 15 minutes) 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 mandatory 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 (FFPE) biopsy samples were used.
The expression profile was to be analysed for correlation with response or resistance to therapy.

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 1 dose of study treatment were included in the Full Analysis (FA) Population. Efficacy analyses were performed on data from all subjects in the FA Population.

- **Safety Population**

All subjects who received at least 1 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 1 quantifiable pre-dose and 1 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, gender, ethnicity, and race. Demographics and baseline characteristics were summarised descriptively. Height and weight were reported with the demographic information listed above. Subject demographics (gender, 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 (SOC) and preferred term (PT). Treatment-related TEAEs, TEAEs leading to death, serious adverse events (SAEs), and TEAEs resulting in study discontinuation were summarised similarly. TEAEs were also summarised by the grade of NCI CTCAE. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) for

purposes of summarization. All TEAEs occurring during the study were included in by-subject data listings and tabulated.

- **Efficacy Analysis**

Response rates were summarized using discrete statistics by disease cohort as well as all disease cohorts combined. Post-treatment RECIST assessments were used to determine best overall response.

PFS was defined as the number of days between the date of the first dose of treatment and the first date of disease progression or death. OS was defined as the number days between the date of the first dose of treatment and the date of death. PFS and OS were estimated using Kaplan-Meier method. The estimated survival probabilities were presented via Kaplan-Meier curves and median survival was reported. The survival analysis was performed by disease cohort as well as all disease cohorts combined.

- **PK Analysis**

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

SUMMARY OF RESULTS AND CONCLUSIONS:

Subject Disposition:

- In Phase 2 and 2 sub-studies, a total of 71 subjects were screened, and 49 subjects were treated with tinostamustine.
- All treated subjects were included in the FA population as well as the Safety Population (n = 49, 100.0% each). In addition, 48 subjects of the Safety Population were included in the PK Population.
- Forty-one (41) subjects (83.7%) discontinued the study treatment. Reasons for study treatment discontinuation were PD (n = 23, 56.1%), subject's decision (n = 7, 17.1%), death (n = 5, 12.2%), TEAE (n = 3, 7.3%), other (n = 2, 4.9%), and Investigator's decision (n = 1, 2.4%).

Demography and Baseline Characteristics:

- Among 49 treated subjects, there were 10 males (20.4%) and 39 females (79.6%), with a median age of 56.0 years (range 28-84). Most of the subjects were aged <65 years (n = 35, 71.4%) and white (n = 40, 81.6%).
- In Phase 2, the cancer diagnoses at baseline included SCLC (4 subjects), STS (10 subjects), TNBC (4 subjects), ovarian cancer (12 subjects), endometrial cancer (6 subjects), in each of the disease cohorts.
- In Sub-study 1, the cancer diagnoses at baseline included breast cancer (2 subjects), endometrial cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer (each 1 subject).
- In Sub-study 2, the cancer diagnoses at baseline included ovarian cancer (2 subjects), adenoid cystic carcinoma, leiomyosarcoma, neuroendocrine carcinoma, non-small cell lung cancer, testis cancer (each 1 subject).

Efficacy Results:

- Of all 49 treated subjects, 1 subject (2.0%) had CR, 2 subjects (4.1%) had PR, 17 subjects (34.7%) had SD as their best overall response. Of these, 16 subjects showed durable SD, who had SD of ≥ 84-day duration. The ORR (CR+PR) was 6.1% (90% confidence interval [CI], 1.7% to 15.1%) and the CBR (CR+PR+durable SD) was 38.8% (90%CI, 27.1% to 51.5%).
- In Phase 2, 1 PR was observed in the STS cohort and the ovarian cancer cohort, respectively. The ORRs (90%CI) were 10.0% (0.5% to 39.4%) in the STS cohort, and 8.3% (0.4% to 33.9%) in the ovarian cancer cohort. In other 3 disease cohorts (SCLC, TNBC, endometrial cancer), CR and PR were not observed. Thirteen (13) SDs of ≥ 84-day duration were observed across the disease cohorts except SCLC. The CBRs (90%CI) were 40.0% (15.0% to 69.6%) in the STS cohort, 50.0% (9.8% to 90.2%) in the TNBC cohort, 50.0% (24.5% to 75.5%) in the ovarian cancer cohort, and 50.0% (15.3% to 84.7%) in the endometrial cancer cohort.

- In Sub-study 1, 1 CR with ovarian cancer and 2 SDs of ≥ 84-day duration were observed. The ORR (90%CI) was 16.7% (0.9% to 58.2%), and the CBR was 50.0% (15.3% to 84.7%). In Sub-study 2, 1 SD of ≥ 84-day duration was observed. The CBR (90%CI) was 14.3% (0.7% to 52.1%).
- For all 49 treated subjects, the median PFS (90%CI) was 78.0 days (56.0 to 101.0).
- In Phase 2, the median PFS (90%CI) was 54.0 days (50.0 to not estimable [NE]) in the SCLC cohort, 56.0 days (50.0 to 236.0) in the STS cohort, 85.0 days (58.0 to NE) in the TNBC cohort, 63.0 days (44.0 to 97.0) in the ovarian cancer cohort, 87.0 days (33.0 to 107.0) in the endometrial cancer cohort. These showed modest efficacy signals of tinostamustine.
- In Sub-study 1, the median PFS (90%CI) was 177.0 days (62.0 to NE). In Sub-study 2, the median PFS (90%CI) was 65.0 days (23.0 to NE).
- For all 49 treated subjects, the median OS (90%CI) was 167.0 days (131.0 to 288.0).
- In Phase 2, the median OS (90%CI) was 114.5 days (85.0 to NE) in the SCLC cohort, 346.5 days (76.0 to NE) in the STS cohort, 218.5 days (58.0 to NE) in the TNBC cohort, 261.0 days (121.0 to NE) in the ovarian cancer cohort, 127.0 days (33.0 to NE) in the endometrial cancer cohort.
- In Sub-study 1, the median OS (90%CI) was 177.0 days (62.0 to NE). In Sub-study 2, the median OS (90%CI) was 139.0 days (23.0 to NE).

PK Results:

- Generally, T_{max} occurred prior to or at the end of the tinostamustine infusion, and $t_{1/2}$ was in the region of 1 hour (in Phase 2 and Sub-study 1) or 2-4 hours (in Sub study 2). Considering the values of AUC_{0-6} and AUC_{0-inf}, the majority of the AUC was observed in the first 6 hours after the start of 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.
- Comparison of the PK concentration profiles between Sub-study 1 (60 mg/m^2 given over 60 minutes) and Sub-study 2 (80 mg/m^2 given over 80 minutes) showed the 80 mg/m^2 dose gives higher concentration data for a longer initial duration, as would be expected of a higher dose administration albeit with a longer infusion duration.
- 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.

Pharmacodynamics Results:

- The gene expression analysis was not conducted because the number of samples was insufficient due to non-mandatory participation.

Safety Results:

TEAEs

- Overall summary of TEAEs was shown below.

	Total (N = 49) n (%)
Subjects with at least one TEAE	48 (98.0)
Subjects with at least one Serious TEAE	24 (49.0)
Subjects with at least one TEAE leading to death	3 (6.1)
Subjects with at least one TEAE resulting in permanent withdrawal of study drug	15 (30.6)
Subjects with at least one Related TEAE	44 (89.8)
Subjects with at least one TEAE of Special Interest	3 (6.1)
Subjects with at least one TEAE leading to dose reduction, interruption, or discontinuation	31 (63.3)
Subjects with at least one TEAE given as primary reason to terminate treatment	3 (6.1)

	Total (N = 49) n (%)
Subjects with at least one TEAE by the worst CTCAE grade	
Grade 1: Mild	2 (4.1)
Grade 2: Moderate	7 (14.3)
Grade 3: Severe	30 (61.2)
Grade 4: Life-threatening	6 (12.2)
Grade 5: Death	3 (6.1)

- TEAEs occurring in ≥20% of subjects were nausea (n = 25, 51.0%), fatigue (n = 17, 34.7%), vomiting, anaemia (n = 16, 32.7% each), thrombocytopenia (n = 13, 26.5%), constipation, diarrhoea (n = 11, 22.4% each), abdominal pain, pyrexia, and headache (n = 10, 20.4% each).
- Treatment-related TEAEs occurring in ≥20% of subjects were nausea (n = 22, 44.9%), thrombocytopenia, fatigue (n = 13, 26.5% each), anaemia (n = 12, 24.5%), and vomiting (n = 11, 22.4%).
- TEAEs leading to death were intra-abdominal haemorrhage, dyspnoea, hypoxia, and cardiac arrest (n = 1, 2.0% each). Of these TEAEs, intra-abdominal haemorrhage was considered related to study drug by the Investigator.
- Serious TEAEs occurring in >1 subject were lymphocyte count decreased, thrombocytopenia, dyspnoea, pleural effusion (n = 3, 6.1% each), platelet count decreased, neutropenia, nausea, small intestinal obstruction, sepsis, acute kidney injury, and infusion related reaction (n = 2, 4.1% each).
- TEAEs resulting in permanent withdrawal of study drug occurring in >1 subject were thrombocytopenia and platelet count decreased (n = 2, 4.1% each).
- TEAEs leading to dose reduction, interruption or discontinuation occurring in >1 subject were thrombocytopenia (n = 9, 18.4%), platelet count decreased, neutropenia (n = 4, 8.2% each), neutrophil count decreased (n = 3, 6.1%), white blood cell count decreased, fatigue and dyspnoea (n = 2, 4.1% each).

QTc prolongations

Based on safety ECGs (standard 12-lead) assessed at each study site

- Three (3) subjects (6.1%) treated in Phase 2 experienced 6 events of electrocardiogram QT prolonged. Two (2) Grade 3 events occurred in one subject, that resulted in dose reduction. The severity of the remaining 4 events were Grade 1 or Grade 2. There was no event leading to dose discontinuation. All 6 events of electrocardiogram QT prolonged were not associated with clinical signs and symptoms.
- The subject who experienced 2 events of Grade 3 electrocardiogram QT prolonged had QTcF >500 msec on Cycle 1 Day 15 and Cycle 2 Day 15. Those ECGs were retrospectively evaluated by a central assessor, as a result, QTcFs >500 msec were not confirmed by central reading.
- The QTcF increased gradually at each post-dose time point on Cycle 1 Day 1 across all Phase 2 cohorts as well as 2 sub-studies. In 47 subjects having the data of QTcF highest increase, the mean of QTcF highest increase (standard deviation) was 38.33 msec (20.523). The QTcF highest increase ≥30 msec was observed in 31 subjects, and ≥60 msec was observed in 3 subjects. No clear differences in QTcF increase were seen between Phase 2 cohorts, Sub-study 1 and Sub-study 2.

Based on Holter ECGs assessed at a central laboratory

- In the cardiac safety analyses of the centrally measured ECG data, the maximal least square (LS) mean change from baseline QTcF (ΔQTcF) on Cycle 1 Day 1 was observed at 45 minutes after start of infusion in each dose group, with 22.5 msec (90% CI: 13.16 to 31.87) for the 60 mg/m^2 in 60 minutes, 27.3 msec (90% CI: 20.83 to 33.68) for the 80 mg/m^2 in 60 minutes, and 18.8 msec

(90% CI: 9.56 to 28.02) for the 80 mg/m^2 in 80 minutes. Overall, the LS mean ΔQTcF tended to increase at higher dose level (80 mg/m^2) or with shorter infusion time (60 minutes). In general, the LS mean ΔQTcF decreased to <20 msec within 2 hours after start of infusion.

- During the tinostamustine infusion itself, there was no evidence of a clinically significant change in heart rate (HR). Maximal increases in LS mean HR of 10-30 beats per minute (bpm) were observed between approximately 3-6 hours after start of infusion on Cycle 1 Day 1. This was unlikely to have been related to a direct effect of tinostamustine on HR, as T_{max} occurred within 1 hour after start of infusion, and $t_{1/2}$ was approximately 1-2 hours on Cycle 1 Day 1.
- There was no evidence of any clinically relevant effect of tinostamustine on atrioventricular conduction as measured by the PR interval, or cardiac depolarization as measured by the QRS duration. There were no new clinically relevant morphological changes demonstrating a signal of concern.
- The concentration-QTc effect modelling analyses confirmed the presence and magnitude of tinostamustine-concentration-dependent effect on QTcF. The dose of tinostamustine 60 or 80 mg/m^2 with 60- or 80-minute infusion can be expected to produce a LS mean QTcF increase of approximately 15-25 msec during the infusion, depending on the dose and infusion time.

Conclusions:
Overall, in these Phase 2 study and 2 sub-studies, tinostamustine had an acceptable safety profile in subjects with advanced solid tumours. The cardiac safety analyses of the centrally measured ECG data indicated the presence of tinostamustine-concentration-dependent effect on QTcF.
The RP2D (80 mg/m^2 of tinostamustine administered over 1 hour on Day 1 and Day 15 of each 4-week treatment cycle) of tinostamustine showed positive efficacy signals in the subjects with advanced solid tumour, especially in the STS cohort and the ovarian cancer cohort. The ORRs (90% CI) and the CBRs (90% CI) were 10.0% (0.5% to 39.4%) and 40.0% (15.0% to 69.6%), respectively in the STS cohort, 8.3% (0.4% to 33.9%) and 50.0% (24.5% to 75.5%), respectively in the ovarian cancer cohort.
The efficacy and safety of the RP2D (80 mg/m^2 of tinostamustine administered over 1 hour on Day 1 and Day 15 of each 4-week treatment cycle) will be further evaluated.

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