A Phase 1 trial to Investigate the Safety, Pharmacokinetic Profiles and the Efficacy of Tinostamustine, a First-in-Class Alkylating Histone Deacetylase Inhibition (HDACi) Fusion Molecule, in Relapsed/Refractory Hematologic Malignancies.

Published: 28-02-2019
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Main objective:1. To estimate the Overall Response Rate (ORR) and the clinical benefit rate in selected cohorts of patients with hematologic malignancies,separately for each cohort2. To evaluate the safety of the selected dose regimes in an expanded...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON52700

Source
ToetsingOnline

Brief title
EDO-S101-1001 study

Condition

- Other condition
- Lymphomas Hodgkin's disease

Synonym

Relapsed/ refractory Hematologic Malignancies

Health condition

relapsed or refractory lymphoid malignancy, relapsed/refractory multiple myeloma, relapsed/refractory Hodgkin□s lymphoma, relapsed/refractory peripheral T-cell lymphoma, relapsed/refractory cutaneous T-cell lymphoma, subtypes mycosis fungoides and Sézary syndrome, relapsed/refractory T-cell Prolymphocytic leukemia. Note: Recruitment to the CTCL and T-PLL cohorts was halted on 01 March 2021.

Research involving
Human

Sponsors and support

Primary sponsor: Mundipharma Research Limited
Source(s) of monetary or material Support: Industry: Mundipharma Research Limited

Intervention

Keyword: EDO-S101, Hematological malignancies, Phase 1

Outcome measures

Primary outcome

This stage of the trial (Stage 2) is designed to determine the objective

response rate (ORR) (complete response [CR] plus partial response

[PR]) and the clinical benefit (CR plus PR plus Stable Disease) separately for

each cohort, and to evaluate the safety of the selected

tinostamustine doses in the lymphoma subtypes and myeloma cohorts.

Six cohorts will be opened:

• Expansion cohort 1: relapsed/refractory MM. Recruitment of patients to this

cohort was halted on 10 December 2021.

• Expansion cohort 2/2A: relapsed/refractory HL.

• Expansion cohort 3: relapsed/refractory PTCL. Recruitment to this cohort was

halted on 01 March 2021.

• Expansion cohort 4: relapsed/refractory CTCL, subtypes mycosis fungoides (MF) and Sézary syndrome (SS).

• Expansion cohort 5: relapsed/refractory T-PLL. Recruitment to this cohort was halted on 01 March 2021.

SAFETY ASSESMENT

Patients will be monitored for safety, toxicity, and efficacy on an ongoing basis. All relevant patient data will be reviewed, including patient clinical status, laboratory values, radiographic scans and adverse events (AEs). The DSMC will provide safety assessments in course of the trial. A first meeting is planned after 20 patients have completed their treatment (up to 6 cycles). The Safety physician or designated physician will inform the committee of important new safety information and facilitate the assessment. The Medical Monitor will inform the committee of treatments' responses or disease progression rates. The roles and responsibilities of the DSMC are outlined in the DSMC Charter.

STOPPING RULES

Stopping rules apply for patients who experience QTc prolongations >500 ms that are not transient or occur in more than 1 cycle.

If the QTcF value on the electrocardiogram (ECG) machine printout is >500 ms or represents an increase > 60 ms from baseline, 2 additional ECGs are to be performed approximately 1 minute apart. If the average QTcF of

the 3 ECGs is >500 ms or increased > 60 ms from baseline, the tinostamustine infusion must be stopped. The patient should stay in the unit until the QTcF has decreased to <=500 ms or is <=60 ms relative to baseline. In addition, the patient is to be continuously observed for syncope or other clinically relevant cardiac events. A thorough evaluation of ECGs and QTc prolongations, including expedited central review by an independent assessor, will be performed. The decision will then be made by the Investigator in consultation with the Medical Monitor, whether tinostamustine treatment is to continue, be postponed, or be stopped.

Secondary outcome

1. To evaluate time to Objective Response (OR) and duration of response (DR).

2. To evaluate the safety of the selected doses in an expanded population of patients with MM and the selected lymphoma subtypes

3. To determine the progression free survival (PFS) time for patients who received the Recommended Phase 2 Dose (RP2D).

4. To determine the overall survival (OS) time for patients who received the RP2D.

5. To further establish the PK profiles of tinostamustine.

6. To perform a concentration corrected QT (QTc) analysis.

Study description

Background summary

The ability to fuse discrete small molecules with different types of pharmacologic activity has created remarkable opportunities in drug discovery

and development. Bendamustine itself is a fusion molecule of the nitrogen mustard mechlroethamine and a purine analog based on fludarabine that exhibits unique activity where cancer cells have become resistant to conventional alkylating agents. In fact, randomized clinical studies have established that the combination of rituximab and bendamustine exhibits less toxicity and greater efficacy of a conventional five drug R-CHOP based regimen. This concept opens the prospect that other rational fusion molecules could exhibit activity even greater than that seen in the parent
molecule. EDO-S101 is a unique new chemical entity that rationally fuses a molecule of vorinostat, an HDAC inhibitor, to the bendamustine backbone. Preclinical studies have unequivocally demonstrated that EDO-S101 exhibits activity greater than that seen with traditional Bendamustine. This clinical trial will represent the first in human experience with this novel first in class drug.

Study objective

Main objective:
1. To estimate the Overall Response Rate (ORR) and the clinical benefit rate in selected cohorts of patients with hematologic malignancies,
separately for each cohort
2. To evaluate the safety of the selected dose regimes in an expanded population of patients with Multiple Myeloma (MM) and the selected lymphoma and leukemia subtypes for which there are no standard therapies available

Secondary objectives:
1. To evaluate time to Objective Response (OR) and duration of response (DR).
2. To evaluate the safety of the selected doses in an expanded population of patients with MM and the selected lymphoma subtypes
3. To determine the progression free survival (PFS) time for patients who received the Recommended Phase 2 Dose (RP2D).
4. To determine the overall survival (OS) time for patients who received the RP2D.
5. To further establish the PK profiles of tinostamustine.
6. To perform a concentration corrected QT (QTc) analysis.

Study design

The study is designed as a two stage Phase 1 trial. Stage 1 of the study is designed to determine the MTD, the optimal infusion time and identify the RP2D (recommended phase 2 dose). Stage 2 of the study is designed to evaluate the safety and efficacy of the selected doses in expansion cohorts of selected hematologic malignancies. Phase 1 of the trial has been completed.

Intervention

100mg/m² of Tinostamustine on D1 of 21d cycle for lymphoma/T-PLL patients and 60mg/m² on D1/D15 of 28d cycle for MM patients.

Study burden and risks

Participants may or may not benefit from the study drug. Other patients with relapsed/refractory hematologic malignancies have the potential to benefit from the development of a possible new treatment. Information collected during the study may increase what doctors know about EDO-S101. As part of the study, the subject will receive EDO-S101 and some tests at no cost.

Disadvantages of participation in the study may be:
- possible side effects of EDO-S101;
- possible adverse effects/discomforts of the evaluations in the study.
Please refer to section E9. "What risks does participation involve for human subjects" for a detailed overview of the risks associated with the study drug and study procedures

Participation in the study also means:
- additional time;
- additional or longer hospital stays;
- additional tests;
- instructions the subject needs to follow

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patient willing and able to sign an informed consent.
2. Patients age >=18 years at signing the informed consent.
3. Life expectancy > 3 months.
4. Diagnosis of relapsed or refractory lymphoid malignancy for which there are no available therapies.
5. Eastern Cooperative Oncology Group (ECOG) performance status <=2.
6. Absolute neutrophil count (ANC) (polymorphonuclear [PMN] cells plus bands) >1,000 / µL.
7. Platelets >= 100,000 / µL.Platelet transfusions within the 14 days before Day 1 of Cycle 1 is prohibited.
8. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) <= 2.5 x ULN.
9. Total bilirubin <2.0 mg/dL unless elevated due to known Gilbert's syndrome.
10. Renal function: estimated creatinine clearance by Cockroft-Gault formula >= 45 mL/min.
11. Serum potassium and magnesium at least at the lowest limit of normal (LLN) range, before every IMP administration; if it is below LNN, supplementation is permissible.
12. Female study participants of childbearing potential, and their partners, and male study participants who intend to be sexually active with a woman of childbearing potential, must be willing to use at least TWO highly effective forms of contraception. For female study participants, this should start from the time of study enrollment and continue throughout tinostamustine administration and for at least six months after the last administration of IMP to be eligible to participate. For male subjects who intend to be sexually active with a women of childbearing potential they must use a condom during treatment and for at least 90 days after the last administration of IMP. Female study participants should be willing to have a pregnancy test performed at screening, <= 1 day prior to day 1 of each IMP administration and at study treatment discontinuation. Vasectomized males are considered fertile; therefore, vasectomized partners and patients must be willing to use a secondary method of effective birth control. Sexual abstinence is considered a

highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Apart from the above general inclusion criteria, there are some criteria that are specific for each cohort, see details in the protocol.

Exclusion criteria

1. Patients with any central nervous system (CNS) involvement.
2. Patient who had a hematologic malignancy that has transformed.
3. Patients who have relapsed within 100 days of stem cell infusion following an autologous or allogeneic bone marrow transplant.
4. Patients with QTc interval (Fridericia*s formula) > 450 msec.
5. Patients who are on treatment with drugs known to prolong the QT/QTc interval. Refer to CredibleMeds list of drugs with known risk of Torsade de pointes (TdP): http://crediblemeds.org
6. Any serious medical condition that interferes with adherence to study procedures.
7. Patients with a history of an other malignancy diagnosed within three (3) years prior to study enrollment excluding basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
8. Pregnant or breast feeding females.
9. New York Heart Association (NYHA) stage III/IV congestive heart failure. The following arrhythmias: atrial fibrillation/flutter with poor rate control, documented sustained ventricular tachycardia (defined as >30 seconds or requiring cardioversion before 30 seconds have elapsed) or Torsades de Pointes.
10. active infections, or other significant co-morbidities [e.g. active central nervous system metastases and/or carcinomatous meningitis, active infection requiring systemic therapy, history of human immunodeficiency virus (HIV) infection, or active Hepatitis B or Hepatitis C].
11. Use of other anti cancer therapies and investigational agents within 28 days prior to the first dose of tinostamustine. After 28 days, patients may be enrolled if they have recovered form any related toxicities >= Grade 1 (except alopecia).
12. Steroid treatment within seven days prior to trial treatment. Patients that require intermittent use of bronchodilators, topical steroids or local steroid injections will not be excluded from the trial. Patients who have been stabilized to 10 mg orally (PO) once daily (QD) or less seven days prior to tinostamustine administration are allowed.

13. Patients on Valproic Acid for any indication (epilepsy, mood disorder) must be excluded from the trial.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	23-07-2020
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tinostamustine
Generic name:	Not applicable

Ethics review

Approved WMO

Date:	28-02-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	25-02-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	19-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	14-01-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-002697-20-NL
ClinicalTrials.gov	NCT02576496
CCMO	NL67414.029.19

Study results

Date completed:	02-11-2023
Results posted:	28-11-2024

First publication
16-12-2022