A Phase I Study to Evaluate the Safety and Tolerability of the Histone Deacetylase Inhibitor, CHR-2845, in Patients with Advanced or Treatment Refractory Haematological Diseases or Lymphoid Malignancies

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Primary objective:* To determine the safety, tolerability, dose-limiting toxicities (DLT), maximum acceptable dose (MAD) and maximum tolerated dose (MTD) of CHR-2845 when administered orally to patients with advanced or treatment refractory...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON33977

Source
ToetsingOnline

Brief title
CHR-2845-001

Condition

- Haematological disorders NEC
- Lymphomas NEC

Synonym
Blood cancer, lymph cancer

Research involving
Human

Sponsors and support

Primary sponsor: Chroma Therapeutics Ltd.
Source(s) of monetary or material Support: Chroma Therapeutics Ltd (Sponsor) will finance this clinical trial.

Intervention

Keyword: Haematological Diseases, Lymphoid Malignancies, Phase I, Safety

Outcome measures

Primary outcome

The primary study parameter is to define the maximum acceptable dose (MAD) and

maximum tolerated dose (MTD).

Secondary outcome

The secundary study parameters are to define the

pharmacokinetics/pharmacodynamics of CHR-2845.

Study description

Background summary

CHR-2845 is a novel type of histone deacetylase inhibitor (HDACi) for use in cancer that, in addition to having broad ranging anti-proliferative activity against transformed cells, is designed to have an increased therapeutic window against diseases which involve cells of the monocyte-macrophage lineage. There are several HDACi*s in clinical development and one, SAHA (Vorinostat, Zolinza®), has recently been approved for use in the treatment of cutaneous T-cell lymphoma. CHR-2845 is a cell-permeant ester that is metabolised to give an active acid, CHR-2847, by the action of an intracellular esterase (human carboxylesterase-1) that is only found in cells of the monocyte lineage. CHR-2847, being a charged molecule, cannot readily leave cells and hence, selectively accumulates in monocytes and macrophages. This results in a 20-100 fold increase in anti-proliferative potency of CHR-2845 for monocytic over non-monocytic tumour cells. This selectivity should lead to an increased

therapeutic window in haematological malignancies involving cells of the monocyte lineage (AML M4, AML M5 and CMML). In addition, there is increasing evidence that macrophages associated with some haematological tumours (tumour-associated macrophages (TAMs)) are involved in supporting the growth and spread of the tumour. This clinical trial will focus on haematological and lymphoid malignancies with the intention of evaluating the safety and tolerability of CHR-2845. Additionally it will compare response in patients where monocytes/macrophages are important disease drivers, with the response in other patients. This will allow an early determination of the potential improvement in therapeutic window afforded by the monocyte/macrophage directed HDACi activity which results from the intracellular accumulation of the active metabolite CHR-2847, compared with the pan-cellular HDACi activity of the parent molecule * CHR-2845.

Study objective

Primary objective:
* To determine the safety, tolerability, dose-limiting toxicities (DLT), maximum acceptable dose (MAD) and maximum tolerated dose (MTD) of CHR-2845 when administered orally to patients with advanced or treatment refractory haematological or lymphoid malignancies

Secondary objectives:
* To determine pharmacokinetic parameters of CHR-2845 and the active metabolite CHR-2847
* To perform a preliminary assessment of the anti-disease activity of CHR-2845 in diseases where monocyte derived cells play an important role versus general haematological malignancies

Study design

This study is an open-label, dose escalating, non-randomised, multi-centre, Phase I study of oral CHR-2845 administered once a day over a 28 day course of treatment. Cohorts of 3 to 6 patients will be treated at increasing dose levels to establish the maximum tolerated dose (MTD) based on the occurrence of DLTs. The study will incorporate two phases for evaluation of dose level: (1) dose escalation over a 28 day duration until the MTD is reached; and (2) evaluation of treatment of up to 12 patients at the MAD. The MTD is defined as the dose at which DLT occurs in two or more patients. The dose below the MTD will be referred to as the maximum acceptable dose (MAD). Pharmacokinetic (PK) analyses will be performed on blood samples taken from all patients in all cohorts. Pharmacodynamic (PD) analyses will be performed on samples taken from all patients in all cohorts.
The maximum volume of blood to be taken from each patient during a one month period for safety, PK and PD evaluation will be 250 mL.
The exact sample size cannot be pre-defined, as the number of patients treated

will depend on the toxicity observed. It is expected that approximately 30 to 36 patients will be enrolled in the study at 5 sites in France, Netherlands and Belgium.

Intervention

Cohorts of 3-6 patients each will be treated with escalating, once daily, oral doses of CHR-2845 to determine the maximum acceptable dose (MAD) based on the occurence of DLTs. There will be two study phases: (a) dose escalation to determine MTD and MAD and (b) expansion of a cohort (max 12 patients) at the maximum acceptable dose level.

Study burden and risks

The potentially expected side effects are listed below:

- During the ECG patients may have mild irritation, slight redness, and itching at the sites on your skin where the recording patches are placed.
- During and after having either blood drawn or a bone marrow aspirate taken patients may experience pain and bruising at the needle site. It is also possible to experience lightheadedness and fainting during or after having blood or bone marrow drawn, and it*s rare but possible for an infection, bleeding or a blood clot to occur.
- Evidence from the available animal safety studies indicates potential side effects that include anaemia, changes in parameters involved in the coagulation of blood and adverse effects on the liver and the thymus. These effects appear to be reversible if treatment is withdrawn in a timely manner.

Burden:

During the study patients will undergo the following assessments:
- Sign informed consent
- Physical Examination
- Performance Status
- Vital signs (incl. length, weight, heart rate, blood pressure, temperature)
- Hematology, Coagulation, Blood chemistry
- Urinalysis
- Chest X-ray
- Disease/tumour measurements
- ECGs
- Blood sampling for pharmacokinetics and pharmacodynamics
- Serum pregnancy test
- Echocardiography
- Bone marrow aspirate
- Complete patient diary (incl. time of study medication intake, dose level, concomitant medication and AEs)

- Patients might be asked to remain in the hospital over night on the evening prior to the first dose of CHR-2845. They will have to remain in the hospital over night until the second day of treatment so that all the necessary remaining ECG recordings and blood samples can be done. On day 28 patients will have the option of remaining in the hospital over night until day 29 of treatment so that all the necessary remaining blood samples can be done.

PK sampling will be done at the following time points (3 mL for each sample):
- day 1: pre-dose (2 samples)
- day 1: 20 min., 1 (2 samples), 2, 4 (2 samples), 6, 8 hours post dose
- day 2: 2 additional blood samples at the 24 hour time point after the first dose
- day 28: pre-dose (2 samples)
- day 28: 20 min., 1 (2 samples), 2, 4 (2 samples), 6, 8 hours post dose
- day 29: One blood sample will be taken (at approximately 24 hours after you have taken the previous dose of CHR-2845)(End of Treatment: 1 PK sample if patient withdrew due to an AE)

PD sampling will be done at the following time points (8 mL for each sample):
- day 1: pre-dose
- day 1: 1 and 4 hours post dose
- day 2: pre-dose (at the 24 hour time point after the first dose)
- day 28: pre-dose
- day 28: 1 and 4 hours post dose

Contacts

Public
Chroma Therapeutics Ltd.

93 Milton Park
OXON OX 14 4RY, Abingdon
United Kingdom
Scientific
Chroma Therapeutics Ltd.

93 Milton Park
OXON OX 14 4RY, Abingdon
United Kingdom

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed, informed consent
2. Histologically or cytologically confirmed malignant haematological disease or lymphoid malignancy refractory to standard therapy or for which no standard therapy exists, including acute leukemias, myelodysplastic syndrome (MDS), Chronic myeloid leukemia (CML), Chronic lymphoid leukemia (CLL), Chronic myelomonocytic leukemia (CMML), multiple myeloma and Non-Hodgkin*s Lymphomas/Hodgkin*s disease
3. Patients shall have recovered from all acute adverse effects of prior therapies, with the exception of alopecia and grade 1 neuropathy where recovery is not required
4. Adequate bone marrow, hepatic and renal function including the following
a. Patients with high blast counts can be included in the trial only if they can be controlled by the use of hydroxyurea (500 mg -3,000 mg daily).
b. Total bilirubin * 1.5 x upper normal limit, excluding cases where elevated bilirubin can be attributed to Gilbert*s Syndrome
c. AST (SGOT), ALT (SGPT) * 2.5 x upper normal limit
d. Creatinine * 1.5 x upper normal limit
5. Age * 18 years
6. Performance status (PS) * 2 - Eastern Cooperative Oncology Group (ECOG) scale
7. Estimated life expectancy greater than 3 months
8. Female patients with reproductive potential must have a negative serum pregnancy test within 7 days prior to start of trial. Both women and men must agree to use a medically acceptable method of contraception throughout the treatment period and for 3 months after discontinuation of treatment. Acceptable methods of contraception include an Intrauterine Device, oral contraceptive, subdermal implant and double barrier (condom with a contraceptive sponge)

Exclusion criteria

1. Patients receiving anti-cancer therapy including chemotherapy, radiotherapy, endocrine therapy, immunotherapy or use of other investigational agents within 21 days prior to trial entry (or a longer period depending on the defined characteristics of the agents used e.g. 6 weeks for mitomycin or nitrosourea, 3 months for antibodies). Bisphosphonates for bone

disease and corticosteroids are permitted provided the dose does not change during the trial. Patients must have recovered from all transient toxicity induced by prior therapy
2. Patients with co-existing active infection, graft versus host disease or serious concurrent illness
3. Patients who have failed to recover from or after a bone marrow transplantation or haematopoietic stem cell transplantation
4. The following diseases are excluded: Burkitt*s lymphoma, primary effusion lymphoma, precursor B-cell lymphoblastic lymphoma, symptomatic central nervous system (CNS) lymphoma, CML blast crisis
5. Patients with significant cardiovascular disease as defined by:
a. history of congestive heart failure requiring therapy
b. history of angina pectoris requiring treatment or myocardial infarction within 6 months prior to trial entry
c. presence of severe valvular heart disease
d. presence of an atrial or ventricular arrhythmia requiring treatment
e. Left Ventricular Ejection Fraction (LVEF) below the normal range at the study centre
f. Uncontrolled hypertension
g. A history of abnormal QTc intervals or an average QTc interval at screening *450 msec
6. Any medical or other condition that in the investigator*s opinion renders the patient unsuitable for this study due to unacceptable risk
7. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or completion of the necessary studies
8. Gastrointestinal disorders that may interfere with absorption of the study drug
9. Patients with known brain tumours or metastases
10. More than 6 prior chemotherapy regimens
11. Patients requiring growth factor support (erythropoietin, Granulocyte/monocyte Colony Stimulating Factor (GM/CSF), etc)
12. Patients requiring palliative radiotherapy within the last 4 weeks prior to study entry
13. Uncontrolled hypercalcaemia (CTCAE v3 grade 2 or higher)
14. Abnormal plasma potassium or magnesium levels (Common Terminology Criteria for Adverse Events (CTCAE) v3 grade 3 or greater) despite therapy
15. Pregnant or breast-feeding women

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-03-2009
Enrollment:	15
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	26-01-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-02-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-12-2009
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	EUCTR2008-005241-27-NL
ClinicalTrials.gov	NCT00820508
CCMO	NL25586.029.08