ISRCTN24989786 https://doi.org/10.1186/ISRCTN24989786

Study of CHR-3996 in combination with tosedostat in subjects with multiple myeloma

Submission date 19/04/2011	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 22/06/2011	**Overall study status** Completed	
Last Edited 10/05/2016	**Condition category** Cancer	

Plain English summary of protocol
http://www.cancerresearchuk.org/cancer-help/trials/a-trial-looking-chr-3996-tosedostat-myeloma

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
HM11/9825

Study information

Scientific Title
A phase I/IIa dose escalation study of CHR-3996 in combination with tosedostat in subjects with relapsed refractory multiple myeloma

Acronym

MUK three

Study objectives
In vitro and in vivo data suggest histone deacetylases (HDAC) inhibitors have an anti-myeloma effect, however it seems unlikely that this class of drugs will be used in the clinics as monotherapy. Phase I studies demonstrate that both CHR-3996 and tosedostat are safe and tolerable when dosed as monotherapy. In addition, there is a strong preclinical rationale supporting the combination of a HDAC inhibitor and aminopeptidase inhibitor in myeloma.

The purpose of this study is therefore to determine the safety and preliminary activity of CHR-3996 administered in combination with tosedostat in subjects with relapsed, refractory multiple myeloma.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Open label multi-centre phase I/IIa trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Multiple myeloma

Interventions
Dose escaltation of CHR-3996 and tosedostat

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
Tosedostat

Primary outcome(s)
1. Dose escalation phase:
1.1. To determine the maximum tolerated dose (MTD) of CHR-3996 and tosedostat, administered in combination, in subjects with relapsed or refractory multiple myeloma.
1.2. We define the MTD to be the dose where at least 2/3 or at least 2/6 patients have a DLT. Therefore the dose taken to the expansion phase will be the MTD-1, or dose level 5 if this highest dose level is reached in the dose escalation phase and no MTD is found. This dose, taken forward to the expansion phase, will be called the recommended dose (RD).

2. Dose expansion phase:
To estimate the response rate (stable disease or better) after four cycles of CHR-3996 and tosedostat at the RD identified in the dose escalation phase

Key secondary outcome(s))
1. To estimate the safety profile of CHR-3996 and tosedostat administered in combination in subjects with relapsed or refractory multiple myeloma
2. To estimate maximum response within six cycles of therapy
3. To estimate maximum response to therapy overall
4. To estimate time to maximum response from therapy
5. To estimate progression-free survival
6. To estimate overall survival
7. To determine the number of patients with CHR-3996 or tosedostat dose reductions
8. To assess compliance to therapy until toxicity, intolerance or progression
9. To assess the pharmacokinetic and pharmacodynamic profile of CHR-3996 when administered in combination with tosedostat

Completion date
01/07/2012

Eligibility

Key inclusion criteria
1. Able to give informed consent and willing to follow study protocol
2. Aged 18 years or over
3. Subjects with multiple myeloma diagnosed according to standard criteria, who have been treated with at least one prior therapy, including bone marrow transplantation (if suitable), and currently requiring further treatment due to relapse or non-response
4. ECOG Performance Status less than or equal to 2
5. Required laboratory values within 14 days prior to registration:
5.1. Absolute neutrophil count >1.0 x 109/L, growth factor support is permitted
5.2. Platelet count >25 x 109/L, platelet support is permitted
5.3. Haemoglobin >8.0g/dL, blood support is permitted
5.4. Bilirubin <2 x upper limit of normal (ULN), excluding cases where elevated bilirubin can be attributed to Gilberts syndrome
5.5. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) <2.5 x ULN; except in subjects with known hepatic involvement, where AST and/or ALT <5.0 x ULN
5.6. Serum creatinine <2.0 x ULN
5.7. Corrected calcium <2.8 mmol/L.
6. Anticipated survival of at least 4 months
7. Evaluable disease per modified International Working Group (IWG) criteria, utilising the following assessments as appropriate:
7.1. Measurement of serum monoclonal protein
7.2. Measurement of serum free light chains
7.3. Measurement of urine M protein (Bence Jones protein) (differential creatinine)
7.4. Detection of plasma cells in bone marrow biopsy or aspirate sample
8. Female subjects of child-bearing potential must have a negative pregnancy test within 24 hours prior to starting therapy and agree to use dual methods of contraception for the duration of the study
9. Male subjects must agree to use a barrier method of contraception for the duration of the study if sexually active with a female of child-bearing potential

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Pregnant (positive pregnancy test) or breastfeeding women
2. Patients with high urinary light chain levels (> 1g/24 hours)
3. Previous anti-tumour therapies, including prior experimental agents or approved anti-tumour small molecules and biologics within 28 days before the start of protocol treatment (or a longer period depending on the defined characteristics of the agents)
4. Steroid therapy to stop rapid relapse during this period is permitted, but must be stopped 7 days prior to study drug administration
5. Bisphosphonates for bone disease and radiotherapy for palliative intent are also permitted
6. Concurrent or previous malignancies (<12 months post end of treatment) at other sites with the exception of appropriately treated localised epithelial skin or cervical cancer
7. Patients with histories (≥12 months) of other tumours may be entered
8. Poorly controlled or serious medical or psychiatric illness that, in the Investigators opinion, is likely to interfere with participation and/or compliance in this clinical study
9. Patients with significant cardiovascular disease (e.g. history of congestive heart failure requiring therapy, presence of severe valvular heart disease, presence of an atrial or ventricular arrhythmia requiring treatment, uncontrolled hypertension, a history of QTc abnormalities or with QTcF intervals >450 msec)
10. Active symptomatic fungal, bacterial, and/or viral infection including active human immunodeficiency virus (HIV) or viral (A, B, or C) hepatitis
11. Gastrointestinal disorders that may interfere with absorption of the study drug
12. Abnormal plasma potassium, calcium or magnesium levels (CTCAE v4 Grade 3 or greater) despite therapy

Date of first enrolment
01/07/2011

Date of final enrolment
01/07/2012

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Clinical Trials Research Unit
Leeds
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Sponsor information

Organisation
University of Leeds (UK)

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

Funder Name
Myeloma UK (UK)

Funder Name
Chroma Therapeutics Ltd (UK)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes