Clinical trial results:
A phase I/II dose escalation trial of HDAC inhibitor Tefinostat (CHR-2845) for cancer associated inflammation in Hepatocellular Carcinoma

Summary

EudraCT number	2012-000326-22
Trial protocol	GB
Global end of trial date	14 December 2017

Results information

Result version number	v1 (current)
This version publication date	27 December 2018
First version publication date	27 December 2018

Trial information

Trial identification

Sponsor protocol code	008260QM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02759601
WHO universal trial number (UTN)	-
Other trial identifiers	CRUK: CRUKD/12/011

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	5 Walden Street, London, United Kingdom, E1 2EF
Public contact	CECM Trials Team, Queen Mary's, University of London, 0044 2078808196, bci-cecmmonitoring@qmul.ac.uk
Scientific contact	CECM Trials Team, Queen Mary's University of London, 0044 2078828196, bci-cecmmonitoring@qmul.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 December 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the safety, tolerability and dose-limiting toxicities (DLT) of tefinostat when administered orally to patients with advanced HCC.
To determine the recommended Phase II dose (RP2D) of tefinostat in patients with advanced HCC.

Protection of trial subjects:

Participant safety was continuously monitored through reporting of adverse events (including dose limiting toxicities), laboratory assessments and physical exams.

Dose Escalation Meetings were convened when each cohort finished recruitment to assess the safety information and to assess if the trial could open to recruitment to the next cohort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 17
Worldwide total number of subjects	17
EEA total number of subjects	17

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	9
From 65 to 84 years	7
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

From December 2012 to September 2016 17 patients with hepatocellular carcinoma (HCC) were enrolled into phase I of the CHR-2845 trial, from 4 centres within the UK. Phase II of the trial was not taken forward.

Pre-assignment

Screening details:

Malignant HCC who have not received prior systemic therapy, with a life expectancy of at least 12 weeks. ECOG performance status of 0-2, and a Child-Pugh classification A or B7. Adequate organ and bone marrow function with no history of cardiovascular disease.

37 patients were screened, and 17 of these patients were deemed to be eligible.

Period 1

Period 1 title	Phase I cohort (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Tefinostat

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Tefinostat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cohort Dose Level	Tefinostat (once or twice daily for 28 day continuous dosing)
0	360mg OD
1	480mg OD
2	240mg BID
3	360mg BID

Number of subjects in period 1	Tefinostat
Started	17
Completed	17

Baseline characteristics

Reporting groups

Reporting group title	Phase I cohort

Reporting group description: -

Reporting group values	Phase I cohort	Total	
Number of subjects	17	17	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	9	
From 65-84 years	7	7	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	3	3	
Male	14	14	
Race Units: Subjects			
White	12	12	
Black (African)	1	1	
Black (Caribbean)	1	1	
Chinese	1	1	
Asian	1	1	
Other (Nepalese)	1	1	
ECOG Performance Status Units: Subjects			
Status 0	11	11	
Status 1	6	6	
Child Pugh Score Points Units: Subjects			
Score 5	8	8	
Score 6	4	4	
Score missing	5	5	
Child Pugh Score Class Units: Subjects			
Class A	17	17	

End points

End points reporting groups

Reporting group title	Tefinostat

Reporting group description: -

Primary: Dose Limiting Toxicity

End point title	Dose Limiting Toxicity[1]

End point description:

To determine the safety, tolerability and dose-limiting toxicities (DLT) of Tefinostat when administered orally to patients with advanced HCC. This will be done by determining causality of each adverse event (AE) to Tefinostat and grading severity according to National Cancer Institute (NCI) CTCAE V4.03. A DLT is defined as an event that is almost certainly/ probably dose-related, and drug related. Patients experiencing any of the following toxicities during the first 28 days of therapy will be considered to have experienced a dose-limiting toxicity (using CTCAE v4.03):
• Absolute Neutrophil Count (ANC) ≤0.5x10 9/L lasting for > 5 days, or ANC ≤ 0.5x109
• Platelet count ≤25x109/L with fever.
• Any other drug-related non-haematological toxicity (CTCAE v4.03 grade 3 or more.
• Inability to tolerate a total of at least a 28 day course of Tefinostat due to toxicity; or any drugrelated adverse event resulting in a more than 14-day treatment delay.

End point type	Primary

End point timeframe:

First 28 days of treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis required. Counts of DLTs provided instead. The maximum tolerated dose (MTD) was defined as 240mg BID (Dose Level 2). However, the recommended phase II dose was 360mg BID (Dose Level 3). Both dose level 2 and 3 were similarly tolerated, as per adverse events reported by each group, however, patients in Dosel level 3 showed better preliminary efficacy data. DLTs seen in Dose level 3 were fatigue (G3 CTCAE) and nausea (G3 CTCAE).

End point values	Tefinostat			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: DLT				
number (not applicable)	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Consent until 28 days after the end of treatment visit.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Tefinostat

Reporting group description: -

Serious adverse events	Tefinostat		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 17 (29.41%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events			
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Abdominal pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bloating			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Tefinostat		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)		
Vascular disorders			
Haemorrhages NEC			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	3		
Portal hypertensions			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Vascular hypertensive disorders NEC			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Surgical and medical procedures			

Surgical and medical procedures subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
General disorders and administration site conditions Asthenic conditions subjects affected / exposed occurrences (all) Body temperature altered subjects affected / exposed occurrences (all) Pain and discomfort NEC subjects affected / exposed occurrences (all)	 15 / 17 (88.24%) 43 1 / 17 (5.88%) 1 3 / 17 (17.65%) 6		
Immune system disorders Atopic disorders subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1		
Reproductive system and breast disorders Reproductive tract signs and symptoms NEC subjects affected / exposed occurrences (all) Vaginal and vulval infections and inflammations subjects affected / exposed occurrences (all)	 2 / 17 (11.76%) 2 1 / 17 (5.88%) 1		
Respiratory, thoracic and mediastinal disorders Coughing and associated symptoms subjects affected / exposed occurrences (all)	 2 / 17 (11.76%) 5		
Psychiatric disorders Disturbances in initiating and maintaining sleep subjects affected / exposed occurrences (all) Sleep disorders NEC	 2 / 17 (11.76%) 2 		

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Speech articulation and rhythm disturbances			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Investigations			
Cholesterol analyses			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Liver function analyses			
subjects affected / exposed	10 / 17 (58.82%)		
occurrences (all)	27		
Mineral and electrolyte analyses			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Physical examination procedures and organ system status			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	5		
Platelet analyses			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	4		
Protein analyses NEC			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	4		
Renal function analyses			
subjects affected / exposed	6 / 17 (35.29%)		
occurrences (all)	14		
Tissue enzyme analyses NEC			
subjects affected / exposed	7 / 17 (41.18%)		
occurrences (all)	9		
Triglyceride analyses			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			

Non-site specific procedural complications			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Skin injuries NEC			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Cardiac disorders			
Dyspnoeas			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	4		
Nervous system disorders			
Headaches			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Nervous System disorder			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	3		
Neurologic visual problems NEC			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Neurological signs and symptoms NEC			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Paraesthesias and dysaesthesias			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Sensory abnormalities NEC			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Anaemias haemolytic immune			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

Haemolyses NEC subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Gastrointestinal disorders Diarrhoea (excl infective) subjects affected / exposed occurrences (all)	5 / 17 (29.41%) 8		
Dyspeptic signs and symptoms subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Gastrointestinal and abdominal pains subjects affected / exposed occurrences (all)	7 / 17 (41.18%) 13		
Gastrointestinal atonic and hypomotility disorders NEC subjects affected / exposed occurrences (all)	5 / 17 (29.41%) 13		
Gastrointestinal dyskinetic disorders subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Gastrointestinal signs and symptoms NEC subjects affected / exposed occurrences (all)	5 / 17 (29.41%) 7		
Nausea and vomiting symptoms subjects affected / exposed occurrences (all)	8 / 17 (47.06%) 27		
Oral dryness and saliva altered subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Oral soft tissue signs and symptoms subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Stomatitis and ulceration subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Skin and subcutaneous tissue disorders			

Dermal and epidermal conditions NEC			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	3		
Pruritus NEC			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	6		
Rashes, eruptions and exanthems NEC			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Renal and urinary disorders			
Genitourinary tract infections and inflammations NEC			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Nephropathies and tubular disorders NEC			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Renal failure and impairment			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Structural and obstructive urethral disorders (excl congenital)			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Urinary abnormalities			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	7		
Urinary tract signs and symptoms NEC			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Endocrine disorders			
Female gonadal function disorders			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Joint related signs and symptoms			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Muscle pains			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Muscle related signs and symptoms NEC			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	5		
Musculoskeletal and connective tissue pain and discomfort			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	9		
Infections and infestations			
Infections NEC			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Lower respiratory tract and lung infections			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Appetite disorders			
subjects affected / exposed	7 / 17 (41.18%)		
occurrences (all)	13		
Carbohydrate tolerance analyses (incl diabetes)			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Diabetes mellitus (incl subtypes)			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Elevated triglycerides			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General nutritional disorders NEC			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hyperglycaemic conditions NEC			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Phosphorus metabolism disorders			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Total fluid volume decreased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Total fluid volume increased			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 August 2012	- Updates to Protocol included changes to the inclusion criteria, kidney related laboratory tests and administrative changes - Updates to Patient Information Sheet and Informed Consent form were administrative clarifications
30 January 2013	- Updates to Protocol included changes to the inclusion criteria, re-wording of a secondary endpoint, information regarding research and safety bloods taken and clarification of responsibilities with regards to SUSAR reporting - Updates to the Patient Information Sheet included changes to ensure document in line with protocol, updates to CT scan timing and amount of blood collected and clarification with regards to future research of translational samples
16 October 2013	- New Investigator Brochure implemented for the IMP.
31 October 2013	- Updates to protocol included changes to inclusion criteria, and minor clarifications regarding registration process and timing of sample collection.
26 September 2014	- Change of Chief Investigator - Updates to Protocol included changes to the eligibility criteria, and changes to biopsies, lab tests and timing of study visits
19 February 2015	- Halt to recruitment - Change of Chief Investigator - Combining of the Patient Information Sheet and Consent Form - Updates to the Protocol included change in the eligibility criteria, biopsies required, study visit frequency, lab tests
23 December 2015	- Release of the temporary halt

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 February 2015	Temporary halt on recruitment.	23 December 2015

Notes:

Limitations and caveats

None reported