



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) $\leq 0.5 \times 10^9/L$ lasting for > 5 days, or $ANC \leq 0.5 \times 10^9$
- Platelet count $\leq 25 \times 10^9/L$ 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 Dose 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 occurrences (all) | 1 / 17 (5.88%) 2 | | |
| Skin injuries NEC subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 2 | | |
| Cardiac disorders Dyspnoeas subjects affected / exposed occurrences (all) | 4 / 17 (23.53%) 4 | | |
| Nervous system disorders Headaches subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | | |
| Nervous System disorder subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 3 | | |
| Neurologic visual problems NEC subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | | |
| Neurological signs and symptoms NEC subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | | |
| Paraesthesias and dysaesthesias subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | | |
| Sensory abnormalities NEC subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | | |
| Anaemias haemolytic immune subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 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 occurrences (all) | 2 / 17 (11.76%) 3 | | |
| Pruritus NEC subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 6 | | |
| Rashes, eruptions and exanthems NEC subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 2 | | |
| Renal and urinary disorders Genitourinary tract infections and inflammations NEC subjects affected / exposed occurrences (all) | 3 / 17 (17.65%) 3 | | |
| Nephropathies and tubular disorders NEC subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | | |
| Renal failure and impairment subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 2 | | |
| Structural and obstructive urethral disorders (excl congenital) subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | | |
| Urinary abnormalities subjects affected / exposed occurrences (all) | 3 / 17 (17.65%) 7 | | |
| Urinary tract signs and symptoms NEC subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | | |
| Endocrine disorders Female gonadal function disorders subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | | |
| Musculoskeletal and connective tissue disorders | | | |

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