



Clinical trial results:

A phase 2 study of the monocyte-targeted histone deacetylase inhibitor tefinostat (CHR-2845) in chronic myelomonocytic leukaemia (CMML)

Summary

EudraCT number	2015-002281-23
Trial protocol	GB
Global end of trial date	31 May 2019

Results information

Result version number	v1 (current)
This version publication date	17 December 2021
First version publication date	17 December 2021
Summary attachment (see zip file)	MONOCLE final report (20211101 Study final report Monocle v1.0.docx)

Trial information

Trial identification

Sponsor protocol code	Spon1345-14
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Additional study identifiers

ISRCTN number	ISRCTN17394489
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cardiff university
Sponsor organisation address	30-36 Newport Road, Cardiff, United Kingdom, CF24 0DE
Public contact	Centre for trials research, Cardiff University, Centre for trials research, Cardiff University, +44 02920687620, ctr@cardiff.ac.uk
Scientific contact	Centre for trials research, Cardiff University, Cardiff University, +44 02920687620, ctr@cardiff.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	01 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 May 2018
Global end of trial reached?	Yes
Global end of trial date	31 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. Is tefinostat (CHR-2845) safe and tolerable for patients with CMML?
2. Is tefinostat clinically effective in CMML? (primary efficacy endpoint will be overall clinical response rate according to the International Consortium MDS/MPN Response Criteria).

Protection of trial subjects:

All subjects remained under the care of a hematological consultant.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 21
Worldwide total number of subjects	21
EEA total number of subjects	0

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)	2
From 65 to 84 years	18
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Recruitment began in January 2017. 21 patients were enrolled into the study, 2 were excluded (one was ineligible and one was recruited in error after recruitment freeze), 19 received at least 1 dose of tefinostat, 1 was excluded from toxicity analysis, 13 were discontinued and then 6 were included in efficacy analysis.

Pre-assignment

Screening details:

The following screening assessments should be performed prior to registration and within 28 days of commencing the first cycle of tefinostat therapy (days -28 to 0): Medical history and demographics, physical examination, ECG, pregnancy test and contraception, hematology, biochemistry, urinalysis, quality of life.

Period 1

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

Arms

Arm title	Tefinostat
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Arm description:

A phase 2 study of the monocyte-targeted histone deacetylase inhibitor tefinostat (CHR-2845) in chronic myelomonocytic leukaemia (CMML).

Arm type	Experimental
Investigational medicinal product name	Tefinostat
Investigational medicinal product code	CHR-2845
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tefinostat will be administered orally on a continuous basis, starting at a once daily dose of 360mg. The dose of tefinostat may be escalated or de-escalated for reasons of tolerability and clinical efficacy.

Number of subjects in period 1 ^[1]	Tefinostat
Started	20
Completed	6
Not completed	14
Ineligible	1
Consent withdrawn by subject	3
Adverse event, non-fatal	5
Lack of efficacy	4
Alternative treatment	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One patient enrolled in the trial was ineligible and therefore was not included in the baseline period.

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	20	20	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	75.4		
standard deviation	± 6.0	-	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	14	14	

Subject analysis sets

Subject analysis set title	Efficacy
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who completed 6 cycles of tefinostat will be included in the efficacy analysis evaluated at the end of cycle 6.

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients who died or withdrew before the end of cycle 2 but not for toxicity reasons, will be excluded from analysis for assessment of the toxicity outcome.

Reporting group values	Efficacy	Safety	
Number of subjects	6	18	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			

Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	75.2 ± 4.1	74.8 ± 6.0	
Gender categorical Units: Subjects			
Female	1	5	
Male	5	13	

End points

End points reporting groups

Reporting group title	Tefinostat
Reporting group description: A phase 2 study of the monocyte-targeted histone deacetylase inhibitor tefinostat (CHR-2845) in chronic myelomonocytic leukaemia (CMML).	
Subject analysis set title	Efficacy
Subject analysis set type	Full analysis
Subject analysis set description: All patients who completed 6 cycles of tefinostat will be included in the efficacy analysis evaluated at the end of cycle 6.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: Patients who died or withdrew before the end of cycle 2 but not for toxicity reasons, will be excluded from analysis for assessment of the toxicity outcome.	

Primary: Safety

End point title	Safety
End point description: Safety and tolerability of tefinostat defined as the proportion of patients experiencing CTC grade 3-4 non-haematological toxicity or death thought to be at least possibly related to tefinostat during the first two cycles of treatment	
End point type	Primary
End point timeframe: During the first two cycles of treatment.	

End point values	Tefinostat	Safety		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	18	18		
Units: Patients				
Unacceptable toxicity	1	1		
Acceptable toxicity	17	17		

Statistical analyses

Statistical analysis title	Safety
Statistical analysis description: It is felt that if more than 40% of patients suffer unacceptable toxicity then the treatment should be rejected, and if fewer than 20% suffer some toxicity then the toxicity profile is considered acceptable.	
Comparison groups	Tefinostat v Safety

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other ^[1]
Parameter estimate	Proportion (95% CI)
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	27.3

Notes:

[1] - Calculated proportion and 95% confidence interval

Primary: Efficacy

End point title	Efficacy
End point description:	
Overall clinical response rate (according to International Consortium MDS/MPN Response Criteria)	
End point type	Primary
End point timeframe:	
Assessed at the end of cycle 6	

End point values	Tefinostat	Efficacy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6	6		
Units: Patients				
Clinical benefit	1	1		
No clinical benefit	5	5		

Statistical analyses

Statistical analysis title	Efficacy
Statistical analysis description:	
The primary clinical efficacy objective of the study is to determine overall response rate after 6 cycles of tefinostat. It is felt that if the overall response rate is below 10% the treatment should be rejected, and if above 30% the treatment is sufficiently promising to warrant further evaluation in a phase III trial.	
Comparison groups	Tefinostat v Efficacy
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other ^[2]
Parameter estimate	Proportion (95% CI)
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	26

Notes:

[2] - Note: Only 6 patients were evaluable for efficacy at the end of cycle 6. The 13 patients who withdrew previously achieved no clinical benefit and are included in the denominator. Thus the proportion is 1/19.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Information about adverse events will be collected and recorded for all patients from the time of start of protocol treatment until 30 days after the last dose of tefinostat therapy.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	All patients receiving at least one dose of tefinostat
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Reporting group description: -

Serious adverse events	All patients receiving at least one dose of tefinostat		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 19 (52.63%)		
number of deaths (all causes)	17		
number of deaths resulting from adverse events			
Investigations			
Gama glutamyl transferase			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	3 / 19 (15.79%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Sore throat			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Kidney infection			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All patients receiving at least one dose of tefinostat		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 19 (100.00%)		
Investigations			
Liver toxicity -Bilirubin			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences (all)	11		
Liver toxicity -ALT			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	9		
Cardiac disorders			
Cardiac Arrhythmia			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	9		
Cardiac function (LVEF)			
subjects affected / exposed	6 / 19 (31.58%)		
occurrences (all)	7		
Cardiac other			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences (all)	12		
General disorders and administration			

site conditions			
Other			
subjects affected / exposed	19 / 19 (100.00%)		
occurrences (all)	71		
Gastrointestinal disorders			
Nausea/vomiting			
subjects affected / exposed	11 / 19 (57.89%)		
occurrences (all)	18		
Oral			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	9 / 19 (47.37%)		
occurrences (all)	10		
Renal and urinary disorders			
Renal toxicity-creatinine			
subjects affected / exposed	18 / 19 (94.74%)		
occurrences (all)	55		
Renal toxicity - proteinuria			
subjects affected / exposed	9 / 19 (47.37%)		
occurrences (all)	24		
Renal toxicity-Haematuria			
subjects affected / exposed	10 / 19 (52.63%)		
occurrences (all)	26		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2017	Update of protocol to version 3.0 - Addition of Urinalysis to the schedule of study assessments
26 January 2018	Update of protocol, PIS 1 and PIS 2. Major changes as a result of an updated IB.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported