Clinical trial results:
Phase II Study of the Tolerability and Efficacy of the Histone Deacetylase Inhibitor Sodium Valproate given in Conjunction with 5-azacytidine and ATRA (all trans retinoic acid) in Patients with Acute Myeloid Leukaemia.

Summary

EudraCT number	2005-000550-75
Trial protocol	GB
Global end of trial date	19 March 2014

Results information

Result version number	v1 (current)
This version publication date	27 February 2020
First version publication date	27 February 2020

Trial information

Trial identification

Sponsor protocol code	RG_05-004

Additional study identifiers

ISRCTN number	ISRCTN68418952
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Vincent Dr., Birmingham, United Kingdom, B15 2TT
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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	23 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the tolerability of four drugs sodium valproate, 5-azacitidine, theophylline and ATRA when administered in combination

Protection of trial subjects:

The study protocol stipulated a strict entry criteria to ensure it was safe for patients to enrol onto the trial and receive therapy. The trial involved more visits to hospital than would usually be required and also extra blood
tests to be performed than in standard clinical care. All patients will benefit from close monitoring during the
trial period. As with all medications, treatment with the trial therapy had potential side effects of which all trial
staff and patients are fully informed. Close monitoring during the treatment period allowed prevention, detection and treatment of these side effects.

Background therapy:

The only treatment provided on the study was the trial therapy (single arm trial).

Evidence for comparator:

N/A

Actual start date of recruitment	22 June 2006
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: 91
Worldwide total number of subjects	91
EEA total number of subjects	91

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)	39
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Trial open to recruitment: 22-Jun-2006. First patient registered 10-Jul-2006. Last patient registered 05-Jan-2012

Pre-assignment

Screening details:

N/A: No screening assessments involved. Please refer to protocol for the eligibility criteria

Pre-assignment period milestones

Number of subjects started	91
Number of subjects completed	79

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Ineligible: 12

Period 1

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

Blinding implementation details:

N/A

Arms

Arm title	Phase II overall period

Arm description:

Experimental arm

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

Dosage and administration details:

Sodium valproate was administered using the regime of 200mg three times a day for 4 days, increasing to 500mg twice a day for the next 4 days and escalating to 3000mg daily or the maximal tolerated dose by increments of 500 mg every four days.

Investigational medicinal product name	All-trans-retinoic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ATRA was administered daily at a dose of 45 mg/m2 daily in 2 divided doses separated by more than 8 hours.

Investigational medicinal product name	Theophylline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule

Routes of administration	Oral use

Dosage and administration details:

Theophylline was administered daily at a dose of 175mg.

Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/skin-prick test
Routes of administration	Subcutaneous use

Dosage and administration details:

Azacitidine was administered subcutaneously at a daily dose of 75/mg2 on the first 7 working days of each cycle (i.e., Mon-Fri administration, Sat-Sun rest days, Mon-Tues administration). Each cycle was every 28 days. Patients received therapy for up to 6 cycles. If they were responding to therapy, treatment was continued.

Number of subjects in period 1[1]	Phase II overall period
Started	79
Completed	16
Not completed	63
Consent withdrawn by subject	2
Physician decision	2
Adverse event, non-fatal	19
Concurrent illness (non-therapy related)	16
Lack of efficacy	24

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: Some of the subjects enrolled to the pre-enrollment period did not reach the baseline period.

Baseline characteristics

End points

End points reporting groups

Reporting group title	Phase II overall period
Reporting group description:	
Experimental arm	

Primary: Assessment of safety of the four drugs, sodium valproate, 5-azacitidine, theophylline and ATRA when administered in combination

End point title	Assessment of safety of the four drugs, sodium valproate, 5-azacitidine, theophylline and ATRA when administered in combination[1]
End point description:	
Discontinuation of trial medication because of treatment-related toxicities	
End point type	Primary
End point timeframe:	
From start of treatment until end of treatment schedule, or patient discontinued 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: The protocol states that data will be presented in a descriptive fashion

End point values	Phase II overall period			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Patients				
Discontinued due to treatment-related toxicities	20			
Did not discontinue due to treatment related toxic	59			

Statistical analyses

No statistical analyses for this end point

Primary: Haematological response

End point title	Haematological response[2]
End point description:	
Response was assessed using the Cheson Criteria (Appendix 6, 7, 8). This will include evidence of a sustained improvement in neutrophil and platelet count, reduction in peripheral blood and bone marrow blast numbers and reduction in platelet and red cell transfusion requirements (where assessable). CR = Complete remission CRi = Complete resmission with incomplete blood count recovery PR = Partial remission	
End point type	Primary
End point timeframe:	
Response was assessed by weekly peripheral blood counts for the first cycle and twice monthly or as clinically indicated thereafter, and bone marrow assessment prior to treatment and at the end of cycles	

1, 2, 3 and 6 of treatment

Notes:

[2] - 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: The protocol states that data will be presented in a descriptive fashion

End point values	Phase II overall period			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Patients				
CR	8			
CRi	7			
PR	11			
Other	53			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the start of study drug treatment until 28 days after the last dose or until the start of other anti-cancer therapy – whichever occurs first.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Phase II overall period

Reporting group description:

Experimental arm

Serious adverse events	Phase II overall period		
Total subjects affected by serious adverse events			
subjects affected / exposed	78 / 79 (98.73%)		
number of deaths (all causes)	73		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Prolonged bleed			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina			

subjects affected / exposed	2 / 79 (2.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Elevated pulse				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Acute coronary syndrome				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hypotension				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Cholecystectomy				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Collapse				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Confusion				

subjects affected / exposed	2 / 79 (2.53%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tremor and unsteadiness				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	2 / 79 (2.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anemia				
subjects affected / exposed	2 / 79 (2.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Blood transfusion				
subjects affected / exposed	3 / 79 (3.80%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Death - AML				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Progressive disease				

subjects affected / exposed	2 / 79 (2.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fever			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Generalised weakness			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	22 / 79 (27.85%)		
occurrences causally related to treatment / all	9 / 22		
deaths causally related to treatment / all	0 / 0		
Tiredness			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Colon carcinoma metastisis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 79 (2.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Painful stools			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Soft stool			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Supportive care			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tongue ulcer			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Rectal bleed			

subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper GI haemorrhage			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Carcinoma of larynx			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Symptom control			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Lower back pain			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anaemia			

subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bilateral pneumonia				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Chest infection				
subjects affected / exposed	5 / 79 (6.33%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile diarrhoea				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Ear infection				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye infection				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				

subjects affected / exposed	20 / 79 (25.32%)			
occurrences causally related to treatment / all	18 / 30			
deaths causally related to treatment / all	1 / 2			
Fungal infection				
subjects affected / exposed	2 / 79 (2.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Infection				
subjects affected / exposed	17 / 79 (21.52%)			
occurrences causally related to treatment / all	14 / 18			
deaths causally related to treatment / all	0 / 1			
Lower respiratory tract infection				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Neutropenic fever				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	15 / 79 (18.99%)			
occurrences causally related to treatment / all	6 / 17			
deaths causally related to treatment / all	3 / 5			
Neutropenic septicaemia				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				

subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	4 / 79 (5.06%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Pyrexia (Influenza)				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Rectal Intersphincteric Fistula				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Shingles				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Swine flu				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Raised calcium levels				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Phase II overall period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 79 (97.47%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Syncope			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	50 / 79 (63.29%)		
occurrences (all)	55		
Feeling unwell			
subjects affected / exposed	10 / 79 (12.66%)		
occurrences (all)	10		
Fever			
subjects affected / exposed	34 / 79 (43.04%)		
occurrences (all)	34		
Insomnia			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	7		
Rigors			
subjects affected / exposed	11 / 79 (13.92%)		
occurrences (all)	11		
Sweating			
subjects affected / exposed	10 / 79 (12.66%)		
occurrences (all)	10		
Weakness			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	7		
Weight loss			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	7		
Body pain			

subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Foot pain			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Pain			
subjects affected / exposed	9 / 79 (11.39%)		
occurrences (all)	10		
Immune system disorders			
Pneumonia			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	19 / 79 (24.05%)		
occurrences (all)	20		
Chest pain			
subjects affected / exposed	8 / 79 (10.13%)		
occurrences (all)	8		
Basal crepitations			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Cough			
subjects affected / exposed	27 / 79 (34.18%)		
occurrences (all)	27		
Dyspnea			
subjects affected / exposed	19 / 79 (24.05%)		
occurrences (all)	19		
Reduced oxygen saturation			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	6		
Wheezing			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Tachycardia			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	7		
Hypotension			
subjects affected / exposed	14 / 79 (17.72%)		
occurrences (all)	14		
Nervous system disorders			
Confusion			
subjects affected / exposed	21 / 79 (26.58%)		
occurrences (all)	24		
Dizziness			
subjects affected / exposed	24 / 79 (30.38%)		
occurrences (all)	26		
Memory loss			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Mood alteration			
subjects affected / exposed	8 / 79 (10.13%)		
occurrences (all)	9		
Somnolence			
subjects affected / exposed	31 / 79 (39.24%)		
occurrences (all)	31		
Speech impairment			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Tremor			
subjects affected / exposed	11 / 79 (13.92%)		
occurrences (all)	11		
Visual Disturbance			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Headache			

subjects affected / exposed	27 / 79 (34.18%)		
occurrences (all)	28		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	49 / 79 (62.03%)		
occurrences (all)	49		
Bruising			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences (all)	6		
Leukopenia			
subjects affected / exposed	43 / 79 (54.43%)		
occurrences (all)	43		
Lymphopenia			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Neutropenia			
subjects affected / exposed	47 / 79 (59.49%)		
occurrences (all)	47		
Thrombocytopenia			
subjects affected / exposed	46 / 79 (58.23%)		
occurrences (all)	46		
Ankle oedema			
subjects affected / exposed	12 / 79 (15.19%)		
occurrences (all)	12		
Leg oedema			
subjects affected / exposed	11 / 79 (13.92%)		
occurrences (all)	12		
Oedema			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Pulmonary oedema			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	5		
Ear and labyrinth disorders			
Blocked/fullness in ears			

subjects affected / exposed	6 / 79 (7.59%)		
occurrences (all)	6		
Deafness			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	38 / 79 (48.10%)		
occurrences (all)	40		
Constipation			
subjects affected / exposed	12 / 79 (15.19%)		
occurrences (all)	13		
Dehydration			
subjects affected / exposed	12 / 79 (15.19%)		
occurrences (all)	13		
Diarrhoea			
subjects affected / exposed	33 / 79 (41.77%)		
occurrences (all)	33		
Haemorrhoids			
subjects affected / exposed	8 / 79 (10.13%)		
occurrences (all)	8		
Heartburn/Dyspepsia			
subjects affected / exposed	11 / 79 (13.92%)		
occurrences (all)	11		
Mouth ulcer			
subjects affected / exposed	10 / 79 (12.66%)		
occurrences (all)	11		
Nausea			
subjects affected / exposed	46 / 79 (58.23%)		
occurrences (all)	46		
Sore mouth			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	7		
Sore throat			
subjects affected / exposed	9 / 79 (11.39%)		
occurrences (all)	9		

Taste alteration			
subjects affected / exposed	15 / 79 (18.99%)		
occurrences (all)	15		
Thirst			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	36 / 79 (45.57%)		
occurrences (all)	36		
Rectal bleeding			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	5		
Abdominal pain			
subjects affected / exposed	21 / 79 (26.58%)		
occurrences (all)	22		
Anus pain			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Mouth pain			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Bruising			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Dry lips			
subjects affected / exposed	16 / 79 (20.25%)		
occurrences (all)	16		
Dry skin			
subjects affected / exposed	16 / 79 (20.25%)		
occurrences (all)	16		
Injection site reaction			
subjects affected / exposed	66 / 79 (83.54%)		
occurrences (all)	71		
Itching			

subjects affected / exposed	11 / 79 (13.92%)		
occurrences (all)	13		
Rash			
subjects affected / exposed	13 / 79 (16.46%)		
occurrences (all)	17		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	7		
Dysuria			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	7		
Urinary frequency			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Urinary retention			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	13 / 79 (16.46%)		
occurrences (all)	13		
Knee pain			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Leg pain			
subjects affected / exposed	9 / 79 (11.39%)		
occurrences (all)	9		
Infections and infestations			
Cellulitis			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences (all)	7		
Chest infection			
subjects affected / exposed	13 / 79 (16.46%)		
occurrences (all)	13		
Febrile neutropenia			

subjects affected / exposed	23 / 79 (29.11%)		
occurrences (all)	23		
Fungal chest infection			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Fungal infection			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Infection			
subjects affected / exposed	8 / 79 (10.13%)		
occurrences (all)	8		
Neutropenic sepsis			
subjects affected / exposed	16 / 79 (20.25%)		
occurrences (all)	16		
Oral thrush			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	7		
URTI			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Elevated ALP			
subjects affected / exposed	10 / 79 (12.66%)		
occurrences (all)	10		
Elevated AST			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Elevated creatinine			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Elevated CRP			
subjects affected / exposed	13 / 79 (16.46%)		
occurrences (all)	13		
Elevated LDH			
subjects affected / exposed	7 / 79 (8.86%)		
occurrences (all)	7		

Elevated urea			
subjects affected / exposed	14 / 79 (17.72%)		
occurrences (all)	14		
Hypoalbuminaemia			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	5		
Hypocalcaemia			
subjects affected / exposed	6 / 79 (7.59%)		
occurrences (all)	6		
Hypokalaemia			
subjects affected / exposed	11 / 79 (13.92%)		
occurrences (all)	11		
Hyponatraemia			
subjects affected / exposed	9 / 79 (11.39%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2006	Amendment of the study title to include the word theophylline to read 'Phase II Study of the Tolerability and Efficacy of the Histone Deacetylase Inhibitor Sodium Valproate given in Conjunction with 5-azacitidine, Theophylline and ATRA (all trans retinoic acid) in patients with Acute Myeloid Leukaemia and High Risk Myelodysplasia.' Addition of John Radcliffe Hospital Oxford as a Participating Centre. The Principal Investigator at Leicester Royal Infirmary has changed from that who was on the original COREC application. The correct version of the patient information sheet has been referenced in the consent form. Minor inconsistencies in the both the protocol and patient information sheet have been corrected.
11 January 2007	The number of patients treated in the study has been increased from 20 to 40 patients. The number of cycles of treatment has also been increased to 6 cycles from 3 cycles. The schedule of events has been amended accordingly and typographical errors to the protocol have been amended. The main changes are a) bone marrow assessments will be performed at screening, at the end of cycle 1, 2, 3 and 6 (5 assessments in total) instead of the 4 assessments done monthly on the current schedule, b) full blood counts are currently done weekly over the 3 cycles of treatment. Following the amendment, we will request a full blood count weekly for the first month and fortnightly thereafter.
21 March 2007	The first cohort of patients on the trial have received azacitidine at 50mg/m2. The next cohort of patients are to receive 75mg/m2 as per protocol. We are requesting that the first cohort of patients treated on the lower dose of azacitidine are allowed to increase their dose in subsequent cycles to 75mg/m2 at the Chief Investigators discretion. This dose of azacitidine has been documented as safe and therapeutic in published studies.
07 January 2009	Extension to recruitment to recruit an additional 30 patients to the study. The treatment schedule has been amended with the aim of optimising the clinical impact of the IMPs.
18 February 2009	Addition of a patient diary that may help patients to record the dose they have been prescribed. Completion of the patient diary is entirely voluntary.
14 October 2009	Study protocol has been amended to clarify when bone marrow assessments are to be done and where they are to be sent, inclusion criteria has been amended. The end of cycle 2 bone marrow assessment will no longer be done and screening bone marrow may be taken within 14 days of starting the trial treatment. Bone marrow samples will now be forwarded to Oxford for analysis and the protocol has clarified the time points at which bone marrow assessments should be done after the initial 6 cycles of treatment. The protocol has also been amended to define reportable SAEs and the patient information sheet has been amended to inform patients that the consent form will be returned to the Sponsor for external monitoring of the consent process.
20 September 2010	The trial was extended to recruit an additional 10 patients in order to understand more clearly response rates in patients who have relapsed after allogeneic stem cell transplantation. It has also been clarified in the main patient information sheet where patient samples will be sent. The two consent forms have been combined into one form.

22 August 2011	The storage conditions for 5-Azacitidine (IMP) have changed and the label and protocol have been amended to reflect this. The protocol has also been amended to clarify the definitions of reportable expected serious adverse reactions. In addition, it has been clarified that bone marrow samples may also be sent to the School of Cancer Sciences, Birmingham for evaluation of epigenetic changes in the patients treated with combined therapy. This has also been clarified in the Patient Information Sheet.
11 January 2012	The 5-Azacitidine used in the above named trial is provided by Ben Venue Laboratories and Celgene Ltd are due to supply clinical trial materials from an alternative manufacturer (Baxter Oncology GmbH, Germany). QP release will still be carried out by Catalent UK Packaging Limited. Almac Clinical Services will also perform QP release for the purpose of this study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23223186