

**Clinical trial results:****RaVvA: Phase II Randomised Trial of 5-Azacitidine versus 5-Azacitidine in combination with Vorinostat in patients with Relapsed Acute Myeloid Leukaemia ineligible for Intensive Chemotherapy****Summary**

EudraCT number	2011-005207-32
Trial protocol	GB
Global end of trial date	31 December 2020

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022
Summary attachment (see zip file)	RAVVA Primary publication_CCR_Aug 2017 (6430.full.pdf) Quality of Life Outcome Data (RAVVA CSR QoL V1.0.pdf)

Trial information**Trial identification**

Sponsor protocol code	RG_11-187
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Additional study identifiers

ISRCTN number	ISRCTN68224706
ClinicalTrials.gov id (NCT number)	NCT01617226
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TT
Public contact	RAVVA Trials Office (Haematology), CRUK Clinical Trials Unit, +44 01213714364, ravva@trials.bham.ac.uk
Scientific contact	RAVVA Trials Office (Haematology), CRUK Clinical Trials Unit, +44 01213714364, ravva@trials.bham.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	16 December 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the activity of azacitidine and vorinostat combined therapy, in terms of overall response (OR) (complete remission (CR), complete remission with incomplete blood count recovery (CRi) and partial remission (PR), as defined by Cheson criteria) and overall survival (OS) in patients with relapsed AML who are ineligible for intensive chemotherapy.

Protection of trial subjects:

Analyses were supplied in confidence to an independent Data Monitoring Committee (DMC), who gave advice on whether the accumulated data from the trial, together with the results from other relevant research, justified the continuing recruitment of further patients. The DMC operated in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC could have considered recommending the discontinuation of the trial if the recruitment rate or data quality were unacceptable or if any issues were identified which may have compromised patient safety. The trial could also have stopped early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community.

A Trial Steering Committee (TSC) provided overall supervision for the trial and provided advice through its independent chair.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 November 2012
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: 259
Worldwide total number of subjects	259
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)	33
From 65 to 84 years	222
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

This trial recruited 259 patients from the UK with newly diagnosed, relapsed, or refractory AML/high risk MDS who were ineligible for intensive chemotherapy.

Pre-assignment

Screening details:

The following tests were performed during screening to ensure the patient was eligible and fit enough to participate in the trial: physical exam (including height, weight, blood pressure and spleen measurement), full blood count, biochemistry, bone marrow, ECG and a pregnancy test (if appropriate).

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Azacitidine alone - control arm

Arm description:

Patients received azacitidine (75mg/m²) by subcutaneous injection on 7 consecutive days (excluding weekends), starting day 1 of 28-day cycles for up to 6 cycles. This was delivered in a 5-2-2 schedule.

Arm type	Active comparator
Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Azacitidine (75mg/m²) by subcutaneous injection on 7 consecutive days (excluding weekends), starting day 1 of 28-day cycles for up to 6 cycles. This should be delivered in a 5-2-2 schedule. Reconstituted azacitidine should be injected subcutaneously into the upper arm, thigh or abdomen. Injection sites should be rotated.

Arm title	Azacitidine + vorinostat
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Arm description:

Patients received (75mg/m²) azacitidine by subcutaneous injection on 7 consecutive days (excluding weekends), starting day 1 of 28-day cycles for up to 6 cycles. Azacitidine should be delivered in a 5-2-2 schedule. Vorinostat (300mg bid) will be taken orally for 7 consecutive days starting on day 3 of each cycle in 28-day cycles for up to 6 cycles. Day 3 is defined as the 3rd day of azacitidine administration.

Arm type	Experimental
Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Azacitidine (75mg/m²) by subcutaneous injection on 7 consecutive days (excluding weekends), starting day 1 of 28-day cycles for up to 6 cycles. This should be delivered in a 5-2-2 schedule. Reconstituted azacitidine should be injected subcutaneously into the upper arm, thigh or abdomen. Injection sites should be rotated.

Investigational medicinal product name	Vorinostat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Vorinostat (300mg bid) will be taken orally for 7 consecutive days starting on day 3 of each cycle in 28-day cycles for up to 6 cycles. Day 3 is defined as the 3rd day of azacitidine administration.

Number of subjects in period 1	Azacitidine alone - control arm	Azacitidine + vorinostat
Started	129	130
Completed	129	130

Baseline characteristics

Reporting groups

Reporting group title	Azacitidine alone - control arm
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Reporting group description:

Patients received azacitidine (75mg/m²) by subcutaneous injection on 7 consecutive days (excluding weekends), starting day 1 of 28-day cycles for up to 6 cycles. This was delivered in a 5-2-2 schedule.

Reporting group title	Azacitidine + vorinostat
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Reporting group description:

Patients received (75mg/m²) azacitidine by subcutaneous injection on 7 consecutive days (excluding weekends), starting day 1 of 28-day cycles for up to 6 cycles. Azacitidine should be delivered in a 5-2-2 schedule. Vorinostat (300mg bid) will be taken orally for 7 consecutive days starting on day 3 of each cycle in 28-day cycles for up to 6 cycles. Day 3 is defined as the 3rd day of azacitidine administration.

Reporting group values	Azacitidine alone - control arm	Azacitidine + vorinostat	Total
Number of subjects	129	130	259
Age categorical			
Units: Subjects			
Less than 70 years old	48	48	96
Greater than or equal to 70 years old	81	82	163
Gender categorical			
Units: Subjects			
Female	54	49	103
Male	75	81	156
Type of disease			
Units: Subjects			
AML	108	109	217
MDS	21	21	42
Stage of Disease			
Units: Subjects			
Newly diagnosed	73	74	147
Relapsed	38	40	78
Refractory	18	16	34
Age - stratification variable			
Units: Subjects			
< 70 years	48	48	96
>=70 years old	81	82	163
Relevant medical history			
Units: Subjects			
Yes	108	115	223
No	21	14	35
Missing	0	1	1
Active Symptoms			
Units: Subjects			
Yes	82	94	176
No	47	35	82
Missing	0	1	1
ECOG performance status			
Units: Subjects			

ECOG 0	52	32	84
ECOG 1	63	70	133
ECOG 2	9	17	26
Missing	5	11	16
ECG result			
Units: Subjects			
Normal	82	87	169
Abnormal	42	38	80
Missing	5	5	10
Bone marrow cellularity			
Units: Subjects			
Hypocellular	24	24	48
Normal	16	12	28
Hypercellular	73	67	140
Not known	15	21	36
Missing	1	6	7
Pulse			
Units: bpm			
arithmetic mean	79.6	82.3	
standard deviation	± 16.5	± 13.5	-
Weight			
Units: Kg			
arithmetic mean	75.5	74.8	
standard deviation	± 14.2	± 15.4	-
Height			
Units: Cm			
arithmetic mean	168.4	168.0	
standard deviation	± 9.3	± 10.4	-
Time from diagnosis			
Units: Months			
arithmetic mean	8.8	7.5	
standard deviation	± 14.8	± 10.2	-
Body surface area			
Units: m2			
arithmetic mean	1.9	1.8	
standard deviation	± 0.2	± 0.3	-
Bone marrow morphology			
Units: % blasts			
arithmetic mean	48.4	44.4	
standard deviation	± 27.8	± 29.1	-
Bone marrow immunophenotyping			
Units: % blasts			
arithmetic mean	38.0	38.1	
standard deviation	± 25.5	± 29.0	-
Bone marrow trephine			
Units: % blasts			
arithmetic mean	44.3	46.6	
standard deviation	± 28.3	± 32.8	-

End points

End points reporting groups

Reporting group title	Azacitidine alone - control arm
Reporting group description: Patients received azacitidine (75mg/m ²) by subcutaneous injection on 7 consecutive days (excluding weekends), starting day 1 of 28-day cycles for up to 6 cycles. This was delivered in a 5-2-2 schedule.	
Reporting group title	Azacitidine + vorinostat
Reporting group description: Patients received (75mg/m ²) azacitidine by subcutaneous injection on 7 consecutive days (excluding weekends), starting day 1 of 28-day cycles for up to 6 cycles. Azacitidine should be delivered in a 5-2-2 schedule. Vorinostat (300mg bid) will be taken orally for 7 consecutive days starting on day 3 of each cycle in 28-day cycles for up to 6 cycles. Day 3 is defined as the 3rd day of azacitidine administration.	

Primary: Overall Response

End point title	Overall Response
End point description:	
End point type	Primary
End point timeframe: Within 6 cycles of treatment	

End point values	Azacitidine alone - control arm	Azacitidine + vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: Number of patients				
Response	53	55		
No Response	76	75		

Statistical analyses

Statistical analysis title	Overall Response
Comparison groups	Azacitidine alone - control arm v Azacitidine + vorinostat
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.84
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.72

Primary: Overall Survival - 1 year

End point title	Overall Survival - 1 year
End point description:	
End point type	Primary
End point timeframe:	
From randomisation until 1 year	

End point values	Azacitidine alone - control arm	Azacitidine + vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: percent				
number (confidence interval 95%)	43.7 (34.9 to 52.2)	42.2 (33.5 to 50.7)		

Statistical analyses

Statistical analysis title	1 year overall survival
Statistical analysis description:	
Kaplan Meir curves were created and log rank tests were used to compare treatment arms and provide point estimates	
Comparison groups	Azacitidine alone - control arm v Azacitidine + vorinostat
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.147
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.48

Secondary: Toxicity - number of patients experiencing a grade 3 or higher adverse event or serious adverse event

End point title	Toxicity - number of patients experiencing a grade 3 or higher adverse event or serious adverse event
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End point description:

End point type	Secondary
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End point timeframe:

Duration of treatment

End point values	Azacitidine alone - control arm	Azacitidine + vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: Number of patients				
Experienced toxicity	107	112		
Not experienced a toxicity	22	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission

End point title	Complete Remission
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End point description:

Complete remission within 6 cycles of treatment as defined by modified Cheson criteria¹ for AML and IWG response criteria for MDS

End point type	Secondary
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End point timeframe:

Within 6 cycles of treatment

End point values	Azacitidine alone - control arm	Azacitidine + vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: Number of patients				
CR	9	14		
CRi or Marrow CR	20	20		
PR	24	21		
Stable Disease	4	6		
Disease Progression	2	1		
Failure or No Response	26	23		
Induction death	20	21		

Missing response	24	24		
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Statistical analyses

No statistical analyses for this end point

Secondary: Dose Intensity

End point title	Dose Intensity
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End point description:

End point type	Secondary
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End point timeframe:

Over all treatment cycles

End point values	Azacitidine alone - control arm	Azacitidine + vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: proportion				
median (inter-quartile range (Q1-Q3))	1.00 (0.99 to 1.01)	1.0 (0.97 to 1.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Medical resource use - days in hospital including SAEs

End point title	Medical resource use - days in hospital including SAEs
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End point description:

End point type	Secondary
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End point timeframe:

From date of randomisation to 6 months post randomisation.

End point values	Azacitidine alone - control arm	Azacitidine + vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: Days				
median (inter-quartile range (Q1-Q3))	10 (4 to 23)	15 (6 to 23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Medical resource use - days in hospital excluding SAEs

End point title	Medical resource use - days in hospital excluding SAEs
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End point description:

End point type	Secondary
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End point timeframe:

From date of randomisation to 6 months post randomisation.

End point values	Azacitidine alone - control arm	Azacitidine + vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: Days				
median (inter-quartile range (Q1-Q3))	15 (6 to 23)	9 (2 to 25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Medical resource - Blood product usage

End point title	Medical resource - Blood product usage
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End point description:

End point type	Secondary
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End point timeframe:

From date of randomisation to 6 months post randomisation.

End point values	Azacitidine alone - control arm	Azacitidine + vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: Units				
median (inter-quartile range (Q1-Q3))				
Blood	15 (7 to 28)	17 (9 to 26)		
Platelets	10 (5 to 21)	8 (4 to 18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Medical resource - day on anti-infectives

End point title	Medical resource - day on anti-infectives
End point description:	
End point type	Secondary
End point timeframe:	
From date of randomisation to 6 months post randomisation.	

End point values	Azacitidine alone - control arm	Azacitidine + vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: Days				
median (inter-quartile range (Q1-Q3))				
Bacterial	53 (25 to 106)	64 (19 to 165)		
Fungal	79 (28 to 188)	121 (20 to 232)		
Viral	111 (20 to 188)	183 (21 to 247)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival - 6 months

End point title	Overall Survival - 6 months
End point description:	
End point type	Secondary
End point timeframe:	
6 months from randomisation	

End point values	Azacitidine alone - control arm	Azacitidine + vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: percent				
number (confidence interval 95%)	69.6 (60.7 to 76.9)	76.3 (67.9 to 82.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival - 24 months

End point title	Overall Survival - 24 months
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation until 24 months	

End point values	Azacitidine alone - control arm	Azacitidine + vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: percent				
number (confidence interval 95%)	20.2 (13.7 to 27.7)	15.4 (9.7 to 22.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Related Toxicity - number of patients experiencing a grade 3 or higher adverse event or serious adverse event

End point title	Treatment Related Toxicity - number of patients experiencing a grade 3 or higher adverse event or serious adverse event
End point description:	
End point type	Secondary

End point timeframe:
During trial treatment

End point values	Azacitidine alone - control arm	Azacitidine + vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: Patients				
Experienced toxicity	63	72		
Not experienced a toxicity	66	58		

Statistical analyses

No statistical analyses for this end point

Secondary: Median duration of response

End point title	Median duration of response
End point description:	
End point type	Secondary
End point timeframe: During treatment for responders	

End point values	Azacitidine alone - control arm	Azacitidine + vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: Months				
number (confidence interval 95%)	10.6 (7.6 to 14.5)	11.3 (8.2 to 16.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of commencement of protocol defined treatment until 28 days after the administration of the last treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Safety Population
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Reporting group description: -

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	193 / 244 (79.10%)		
number of deaths (all causes)	232		
number of deaths resulting from adverse events			
Vascular disorders			
Haematoma			
subjects affected / exposed	3 / 244 (1.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thromboembolic event			
subjects affected / exposed	2 / 244 (0.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	2 / 244 (0.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Fatigue				
subjects affected / exposed	2 / 244 (0.82%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	25 / 244 (10.25%)			
occurrences causally related to treatment / all	32 / 33			
deaths causally related to treatment / all	2 / 2			
Flu like symptoms				
subjects affected / exposed	1 / 244 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions - Other, specify				
subjects affected / exposed	2 / 244 (0.82%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Injection site reaction				
subjects affected / exposed	1 / 244 (0.41%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Localised edema				
subjects affected / exposed	1 / 244 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	1 / 244 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 244 (0.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Sudden death NOS				

subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Social circumstances			
Social circumstances - Other, specify			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Reproductive system and breast disorders - Other, specify			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnea			
subjects affected / exposed	5 / 244 (2.05%)		
occurrences causally related to treatment / all	2 / 7		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	5 / 244 (2.05%)		
occurrences causally related to treatment / all	5 / 7		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			

subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleuritic pain			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pulmonary edema			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory failure			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders - Other, specify			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusion			
subjects affected / exposed	2 / 244 (0.82%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hallucinations			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			

Creatinine increased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	4 / 244 (1.64%) 2 / 5 0 / 0		
Electrocardiogram QT corrected interval prolonged subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 244 (0.41%) 1 / 1 0 / 0		
INR increased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 244 (0.41%) 0 / 1 0 / 0		
Platelet count decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 244 (1.23%) 3 / 3 0 / 0		
Injury, poisoning and procedural complications Fracture subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 244 (0.41%) 0 / 1 0 / 0		
Cardiac disorders Acute coronary syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 244 (0.41%) 0 / 1 0 / 0		
Atrial fibrillation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	4 / 244 (1.64%) 3 / 4 0 / 0		
Chest pain - cardiac			

subjects affected / exposed	6 / 244 (2.46%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Heart failure			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 244 (0.82%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	3 / 244 (1.23%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Intracranial hemorrhage			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Lethargy			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			

subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Stroke			
subjects affected / exposed	2 / 244 (0.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	4 / 244 (1.64%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 244 (1.23%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders - Other, specify			
subjects affected / exposed	3 / 244 (1.23%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	76 / 244 (31.15%)		
occurrences causally related to treatment / all	139 / 145		
deaths causally related to treatment / all	3 / 4		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 244 (1.23%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Anal pain			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Colonic hemorrhage				
subjects affected / exposed	1 / 244 (0.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	10 / 244 (4.10%)			
occurrences causally related to treatment / all	6 / 10			
deaths causally related to treatment / all	1 / 1			
Diarrhoea				
subjects affected / exposed	12 / 244 (4.92%)			
occurrences causally related to treatment / all	9 / 14			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	2 / 244 (0.82%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Fecal incontinence				
subjects affected / exposed	1 / 244 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders - Other, specify				
subjects affected / exposed	1 / 244 (0.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	1 / 244 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	5 / 244 (2.05%)			
occurrences causally related to treatment / all	6 / 7			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				

subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stomach pain			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 244 (0.82%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	10 / 244 (4.10%)		
occurrences causally related to treatment / all	9 / 12		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Rash acneiform			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	2 / 244 (0.82%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 244 (1.64%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	1 / 2		

Haematuria			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders - Other, specify			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 244 (1.23%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Chest wall pain			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint effusion			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscle weakness lower limb			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders - Other, specify			
subjects affected / exposed	2 / 244 (0.82%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Soft tissue necrosis lower limb			

subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Device related infection			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations - Other, specify			
subjects affected / exposed	3 / 244 (1.23%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations - Not listed			
subjects affected / exposed	25 / 244 (10.25%)		
occurrences causally related to treatment / all	31 / 31		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	2 / 244 (0.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Mucosal infection			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	50 / 244 (20.49%)		
occurrences causally related to treatment / all	51 / 59		
deaths causally related to treatment / all	2 / 5		
Sinusitis			

subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory infection			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 244 (0.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 244 (0.82%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			

subjects affected / exposed	1 / 244 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	2 / 244 (0.82%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	152 / 244 (62.30%)		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	54 / 244 (22.13%)		
occurrences (all)	298		
Platelet count decreased			
subjects affected / exposed	65 / 244 (26.64%)		
occurrences (all)	530		
White blood cell count decreased			
subjects affected / exposed	35 / 244 (14.34%)		
occurrences (all)	216		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	43 / 244 (17.62%)		
occurrences (all)	248		
Febrile neutropenia			
subjects affected / exposed	28 / 244 (11.48%)		
occurrences (all)	120		
Infections and infestations			
Sepsis			
subjects affected / exposed	13 / 244 (5.33%)		
occurrences (all)	32		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2012	References to Phase I have been removed; vorinostat dose in combination with azacitidine has been stipulated as 300mg bid; monitoring of PT and INR for patients administered warfarin concomitantly with vorinostat; monitoring of serum glucose for patients administered vorinostat; bone marrow sample required for Leukaemic Stem Cell Quantification has been stipulated as at least 6mls; Adverse Event reporting relating to pregnancy includes requesting information to be collected from patients who become pregnant on trial as well as partners of patients who become pregnant whilst the patient is on trial.
03 January 2013	Primary outcome measure further clarified; exclusion criterion amended; screening assessment to include research bone marrow sample; azacitidine administration schedule is further clarified; sample collection section amended to include additional samples; patient follow up further clarified.
10 April 2013	Patient inclusion criteria amended to include patients with newly diagnosed, refractory AML and high risk MDS; IWG response criteria to be used for MDS; Females of childbearing potential to use contraception for 90 days after treatment discontinuation; Stratification will be used to randomise patients to treatment; Trial Steering Committee membership has been amended; Test for Primary Outcome Measure Analysis has been changed.
14 May 2014	AML response criteria has been modified to remove platelet and neutrophil count requirements for Partial Remission (PR) criteria (Appendix 8); Quality of Life questionnaire completion time-points have been clarified (monthly for the first 6 months and then at 12 and 24 months); Medical resource use data collection has been amended (data to be collected until 6 months follow up); Exclusion criteria amended, (removal of autologous haematopoietic stem cell transplant); Inclusion of home administration of azacitidine; Patients continuing beyond 6 cycles, treatment can be adjusted up to 6-weekly cycles at the discretion of the Investigator; Quality of Life questionnaire at screening has been removed (section 5.1); Treatment schedule has to be followed until treatment discontinuation; Blood biochemistry, haematology and bone marrow assessment results can be obtained locally if results are available (section 7.3); Follow up section amended; An aliquot from the blood sample will be sent for central HLA tissue typing and delivery method of samples has been amended (section 7.4.1); Adverse Event reporting has been amended (see section 8.1.1); Appendix 7 (IPSS table) corrected.
14 August 2014	The sample size calculation has been amended and the recruitment has been increased to 260 patients. A copy of the Quality of Life questionnaires are to be kept by sites.
28 November 2014	Requirement of sites to keep a copy of Quality of Life questionnaires has been removed. Additional wording of bone marrow samples to be sent every 3 cycles post cycle 6 (section 7.4.2). Adverse event reporting has been amended (section 8.1). Physical examination can be done within 7 days prior to start of cycle (section 7.3). Physical examination no longer required at end of treatment (section 7.2).
20 April 2015	Extension of study to 37 months. Patient's on 6 weekly cycles to have day 22 bloods on day 36. Change to dose modifications on the combined arm (section 7.5). Updated trial office contact details. Addition of wording to trial treatment regarding unit closures (section 7.1).

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/28765326>