Clinical trial results:
A phase II study of the use of azacitidine for the treatment of patients with chronic graft-versus-host-disease who have failed therapy with corticosteroids

Summary

EudraCT number	2014-005659-19
Trial protocol	GB
Global end of trial date	18 August 2020

Results information

Result version number	v1 (current)
This version publication date	05 August 2021
First version publication date	05 August 2021

Trial information

Trial identification

Sponsor protocol code	RG_14-287

Additional study identifiers

ISRCTN number	ISRCTN15649711
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TH
Public contact	Sonia Fox, University of Birmingham, 0044 01214159181, aztec@trials.bham.ac.uk
Scientific contact	Sonia Fox, University of Birmingham, 0044 01214159181, aztec@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	18 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 August 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the safety and activity (in terms of best overall response within 6 months) of azacitidine in the treatment of patients with cGVHD who have failed therapy with corticosteroids

Protection of trial subjects:

Azactidine is licensed for use in intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS), chronic myelomonocytic leukaemia (CMML) with 10-29 % marrow blasts without myeloproliferative disorder and acute myeloid leukaemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification. Azacitidine has been used following allogeneic stem cell transplantation (ASCT) in clinical trials as maintenance therapy. To our knowledge, it has not been used to treat patients with cGvHD. The dose of azacitidine planned in the AZTEC trial is the same as the dose stipulated in published data of patients who have received a ASCT (i.e. roughly half the dose used in standard practice - 36mg/m2 rather than 75mg/m2
given over 5 days rather than 7 days). In standard practice azacitidine is injected subcutaneously, whereas in this trial it can be administered either by subcutaneous injections or via intravenous infusion (IV). The option of the IV route is because subcutaneous injection often causes a reaction at the injection site. As there is a strong likelihood that some of this patient population will have severe skin complications; it is considered safer to administer the azacitidine intravenously to these patients. The safety profile of azacitidine is well understood and all participating sites will be familiar with expected adverse reactions (ARs) and their management.
Detailed information was described in the protocol to decrease the incidence of any and relieve the symptoms of possible unwanted events.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 October 2015
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: 14
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	12
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Fifteen patients were registered to the trial, of which, 14 patients are evaluable and data for 14 patients will be presented. A single patient was found to be ineligible post randomisation and therefore was withdrawn from the trial.

Pre-assignment

Screening details:

Screening commenced following consent and prior to patient registration in order to confirm eligibility. The Investigator will conduct a full screening evaluation to ensure that the patient satisfies all inclusion and exclusion criteria. Detailed screening formation was described in the protocol.

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	Registered patients

Arm description:

Patients will receive treatment with 36mg/m2 of azacitidine of days 1-5 of each cycle. Each cycle will last 28 days. Azacitidine may be administered via subcutaneous injection or intravenously to avoid potential complications of administering subcutaneously if the patient has extensive skin cGvHD. If a patient starts treatment with azacitidine being administered intravenously but subsequently can tolerate subcutaneous injection then the method of administration can be changed. This also applies if the patient starts on subcutaneous injection but can no longer tolerate this, the administration can be changed to intravenous. Patients will receive 6 cycles of azacitidine treatment. Patients may continue beyond 6 cycles (maximum of 10) if clinical benefit is observed.

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

Dosage and administration details:

Patients will receive treatment with 36mg/m2 of azacitidine of days 1-5 of each cycle. Each cycle will last 28 days. Azacitidine may be administered via subcutaneous injection or intravenously to avoid potential complications of administering subcutaneously if the patient has extensive skin cGvHD.
The dose of azacitidine to be administered should be calculated based upon the patient's body surface area (BSA).
Method of subcutaneous injection:
Reconstituted azacitidine should be injected subcutaneously into the upper arm, thigh or abdomen. Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red or hardened.

Method of infusion:
The total dose of azacitidine should be administered over a period of 10-40 minutes. Please note the administration must be completed within 1 hour of reconstitution.

Number of subjects in period 1	Registered patients
Started	14
Completed	14

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	14	14	
Age categorical Units: Subjects			
Adults (18-64 years)	12	12	
From 65-84 years	2	2	
Gender categorical Units: Subjects			
Male	14	14	
Progression of Chronic GvHD on 1 mg/kg/day prednisolone over 2 weeks. Units: Subjects			
No	14	14	
Stable Chronic GvHD on ≥ 0.5mg/kg/day prednisolone over 4 Units: Subjects			
No	14	14	
Inability to taper prednisolone below 0.5mg/kg/day without recurrence of clinical manifestations. Units: Subjects			
No	4	4	
Yes	10	10	
Inability to tolerate first line therapy (eg steroid myopathy, calcineurin inhibitor-induced renal t Units: Subjects			
No	11	11	
yes	3	3	
Progressive, recurrent or delayed-onset Acute GvHD Units: Subjects			
no	9	9	
yes	5	5	
Type of steroid Units: Subjects			
IV Methylprednisolone	1	1	
None	1	1	
Prednisolone	12	12	
Prednisolone Dose Units: Subjects			
0.63 mg/kg	1	1	
1 mg/kg	9	9	
2 mg/kg	1	1	

unknown	3	3	
Methylprednisolone Dose Units: Subjects			
2 mg/kg	14	14	
Patient come off immune suppression Units: Subjects			
yes no	4 10	4 10	
Immunosuppressive Agent Units: Subjects			
Ciclosporin Tacrolimus none	9 2 3	9 2 3	
Medical conditions Units: Subjects			
No yes	8 6	8 6	
Diabetes Units: Subjects			
Yes no	4 10	4 10	
CardiacProblem Units: Subjects			
yes no	3 11	3 11	
Asthma Units: Subjects			
yes No	2 12	2 12	
Lung Disease Units: Subjects			
yes no	3 11	3 11	

Subject analysis sets

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The population for analysis is defined as modified-intention-to-treat (mITT). This includes only evaluable patients and a patient becomes evaluable when they have completed one cycle of treatment.

Reporting group values	mITT		
Number of subjects	14		
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years	12 2		
Gender categorical Units: Subjects			
Male	14		

Progression of Chronic GvHD on 1 mg/kg/day prednisolone over 2 weeks. Units: Subjects			
No	14		
Stable Chronic GvHD on ≥ 0.5mg/kg/day prednisolone over 4 Units: Subjects			
No	14		
Inability to taper prednisolone below 0.5mg/kg/day without recurrence of clinical manifestations. Units: Subjects			
No	4		
Yes	11		
Inability to tolerate first line therapy (eg steroid myopathy, calcineurin inhibitor-induced renal t Units: Subjects			
No	12		
yes	3		
Progressive, recurrent or delayed-onset Acute GvHD Units: Subjects			
no	10		
yes	5		
Type of steroid Units: Subjects			
IV Methylprednisolone	1		
None	1		
Prednisolone	13		
Prednisolone Dose Units: Subjects			
0.63 mg/kg	1		
1 mg/kg	9		
2 mg/kg	1		
unknown	3		
Methylprednisolone Dose Units: Subjects			
2 mg/kg	1		
Patient come off immune suppression Units: Subjects			
yes	4		
no	11		
Immunosuppressive Agent Units: Subjects			
Ciclosporin	9		
Tacrolimus	2		
none	3		
Medical conditions Units: Subjects			
No	9		
yes	6		
Diabetes			

Units: Subjects			
Yes	4		
no	10		
CardiacProblem Units: Subjects			
yes	3		
no	11		
Asthma Units: Subjects			
yes	2		
No	12		
Lung Disease Units: Subjects			
yes	3		
no	11		

End points

End points reporting groups

Reporting group title	Registered patients

Reporting group description:

Patients will receive treatment with 36mg/m2 of azacitidine of days 1-5 of each cycle. Each cycle will last 28 days. Azacitidine may be administered via subcutaneous injection or intravenously to avoid potential complications of administering subcutaneously if the patient has extensive skin cGvHD. If a patient starts treatment with azacitidine being administered intravenously but subsequently can tolerate subcutaneous injection then the method of administration can be changed. This also applies if the patient starts on subcutaneous injection but can no longer tolerate this, the administration can be changed to intravenous. Patients will receive 6 cycles of azacitidine treatment. Patients may continue beyond 6 cycles (maximum of 10) if clinical benefit is observed.

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The population for analysis is defined as modified-intention-to-treat (mITT). This includes only evaluable patients and a patient becomes evaluable when they have completed one cycle of treatment.

Primary: Best overall response

End point title	Best overall response

End point description:

Best overall response (complete or partial) (GvHD) within 6 cycles of trial treatment as defined by modified National Institutes of Health (NIH) Consensus Response Criteria

End point type	Primary

End point timeframe:

Within 6 cycles of treatment

End point values	Registered patients	mITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	14		
Units: integer				
Overall Response (CR/PR)	7	7		
Complete Response (CR)	1	1		
Partial Response (PR)	6	6		
No Response (NR)	7	7		

Statistical analyses

Statistical analysis title	Overall Response
Comparison groups	Registered patients v mITT

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	50
Confidence interval	
level	95 %
sides	2-sided
lower limit	23
upper limit	77

Statistical analysis title	Complete Response
Comparison groups	Registered patients v mITT
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	34

Statistical analysis title	Partial Response
Comparison groups	Registered patients v mITT
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	43
Confidence interval	
level	95 %
sides	2-sided
lower limit	18
upper limit	71

Statistical analysis title	No Response
Comparison groups	Registered patients v mITT

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	50
Confidence interval	
level	95 %
sides	2-sided
lower limit	23
upper limit	77

Primary: Tolerability of azacitidine

End point title	Tolerability of azacitidine

End point description:

Tolerability of azacitidine defined as the absence of grade 3 or 4 clinically relevant and drug related adverse events (AEs) resulting in stopping treatment early including treatment related deaths within 6 cycles of trial treatment

End point type	Primary

End point timeframe:

Within 6 cycles of treatment

End point values	Registered patients	mITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	14		
Units: integer	13	13		

Statistical analyses

Statistical analysis title	Tolerability of azacitidine
Comparison groups	Registered patients v mITT
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	93
Confidence interval	
level	95 %
sides	2-sided
lower limit	66
upper limit	100

Secondary: Best overall response	
End point title	Best overall response
End point description:	
Best overall response (complete or partial) (GvHD) between registration and 6 months post end of trial treatment as defined by modified National Institutes of Health (NIH) Consensus Response Criteria	
End point type	Secondary
End point timeframe:	
Between registration and 6 months post end of trial treatment	

End point values	Registered patients	mITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	14		
Units: integer				
Overall Response (CR/PR)	8	8		
Complete Response (CR)	5	5		
Partial Response (PR)	3	3		
No Response (NR)	6	6		

Statistical analyses

Statistical analysis title	Overall Response
Comparison groups	Registered patients v mITT
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	57
Confidence interval	
level	95 %
sides	2-sided
lower limit	29
upper limit	82

Statistical analysis title	Complete Response
Comparison groups	Registered patients v mITT
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	36

Confidence interval	
level	95 %
sides	2-sided
lower limit	13
upper limit	65

Statistical analysis title	Partial Response
Comparison groups	Registered patients v mITT
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	21
Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	51

Statistical analysis title	No Response
Comparison groups	Registered patients v mITT
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	43
Confidence interval	
level	95 %
sides	2-sided
lower limit	18
upper limit	71

Secondary: Best organ level response	
End point title	Best organ level response
End point description:	
Best organ level response (GvHD) between registration and 6 months post end of trial treatment as determined by the incremental improvement and changes in individual organ systems involved in cGvHD according to modified NIH Consensus Response Criteria.	
End point type	Secondary
End point timeframe:	
Between registration and 6 months post end of trial treatment	

End point values	Registered patients	mITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	14		
Units: integer				
Complete Response	4	4		
Partial Response	4	4		
Organ Progression	2	2		
No Response	4	4		

Statistical analyses

Statistical analysis title	Complete Response
Comparison groups	Registered patients v mITT
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	29
Confidence interval	
level	95 %
sides	2-sided
lower limit	8
upper limit	58

Statistical analysis title	Partial Response
Comparison groups	Registered patients v mITT
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	29
Confidence interval	
level	95 %
sides	2-sided
lower limit	8
upper limit	58

Statistical analysis title	Organ Progression
Comparison groups	Registered patients v mITT

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	14
Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	43

Statistical analysis title	No Response
Comparison groups	Registered patients v mITT
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	29
Confidence interval	
level	95 %
sides	2-sided
lower limit	8
upper limit	58

Secondary: Duration of response

End point title	Duration of response

End point description:

The median duration of response is presented. 95% confidence interval is also presented but the upper limit cannot be estimated due to small numbers.

End point type	Secondary

End point timeframe:

This will be measured from date of response to date of progression or date last seen for patients who do not progress during the trial

End point values	Registered patients	mITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	8		
Units: time				
number (confidence interval 95%)	4.7 (1.0 to 5)	4.7 (1 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in corticosteroid dosage

End point title	Reduction in corticosteroid dosage

End point description:

End point type	Secondary

End point timeframe:

Percentage change from baseline in corticosteroid dosage at the end of six cycles of trial treatment will be presented along with the 95% confidence interval

End point values	Registered patients	mITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	7	7		
Units: integer				
End of 6 cycles	7	7		

Statistical analyses

Statistical analysis title	End of 6 cycles
Comparison groups	Registered patients v mITT
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	72
Confidence interval	
level	95 %
sides	2-sided
lower limit	33
upper limit	100

Secondary: Reduction in corticosteroid dosage

End point title	Reduction in corticosteroid dosage

End point description:

End point type	Secondary

End point timeframe:

Percentage change from baseline in corticosteroid dosage at 6 months post end of trial treatment will be presented along with the 95% confidence interval.

End point values	Registered patients	mITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: integer				
6 months post end of trial treatment	11	11		

Statistical analyses

Statistical analysis title	6 months post end of trial treatment
Comparison groups	Registered patients v mITT
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	proportion
Point estimate	78
Confidence interval	
level	95 %
sides	2-sided
lower limit	56
upper limit	100

Secondary: Quality of Life

End point title	Quality of Life
End point description:	
FACT-BMT Total Score and Lee Symptom Total Score are presented	
End point type	Secondary
End point timeframe:	
Between registration and 6 months post end of trial treatment	

End point values	Registered patients	mITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	14		
Units: integer				
FACT-BMT Total Score	14	14		
Lee Symptom Total Score	14	14		

Statistical analyses

Statistical analysis title	FACT-BMT Total Score
Comparison groups	Registered patients v mITT
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006
Method	Mixed models analysis
Parameter estimate	coefficient
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.61

Statistical analysis title	Lee Symptom Total Score
Comparison groups	Registered patients v mITT
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.199
Method	Mixed models analysis
Parameter estimate	coefficient
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.17

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Details of all AEs (except those listed above) were to be documented and reported from the date of commencement of protocol defined treatment until 28 days after the administration of the last treatment.

Adverse event reporting additional description:

SAEs that were at least possibly related to azacitidine were reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Safety Population

Reporting group description: -

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	1		
Investigations			
Investigations			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Platelet count decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Vascular disorders			
Vascular disorders			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Neuralgia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vomiting			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Productive cough			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusion			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorder			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Sinusitis			

subjects affected / exposed	1 / 14 (7.14%)		
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	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
General disorders and administration site conditions			
Flu like symptoms			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Injection site reaction			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Multi-organ failure			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Dyspnea			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Psychiatric disorders			

Agitation subjects affected / exposed occurrences (all) Restlessness subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Investigations Neutrophil count decreased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) White blood cell decreased subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 5 2 / 14 (14.29%) 5 1 / 14 (7.14%) 2		
Nervous system disorders Encephalopathy subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all) Neuralgia subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Eye disorders Retinal vascular disorder subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		

Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Nausea subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Vomiting subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Skin and subcutaneous tissue disorders			
Dry skin subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Pain of skin subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 3		
Pruritus subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Rash maculo-papular subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Skin and subcutaneous tissue disorder subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Renal and urinary disorders			
Acute kidney injury subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Chronic kidney disease subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Musculoskeletal and connective tissue disorders			
Flank pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		

Musculoskeletal and connective tissue disorder			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	3		
Infections and infestations			
Bladder infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Lung infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Sepsis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypocalcemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypokalemia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2016	Change to the time point the first research sample is taken. Change to the route of administration of azacitidine from remaining consistent per patient throughout the trial to allowing the route to be changed during treatment. Update to NIH chronic GvHD assessment for Clinician use Update to lung function tests
11 July 2017	Clarification of permitted delays to treatment. Change to the lung function tests. Change to the units used to measure Liver total bilirubin in the NIH chronic GvHD assessment form. Clarification of statistical analysis of primary and secondary outcome measures, population for analysis and interim and final analysis, Addition of units for the baseline only values in the NIH chronic GvHD assessment form v3.0 17-Jan-2018.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported