Clinical trial results:
Bubble: Phase 1B Study of buparlisib with Bortezomib in Defined Genetic Subgroups of Patients with Relapsed or Refractory Multiple Myeloma

Summary

EudraCT number	2014-002477-10
Trial protocol	
Global end of trial date	09 April 2020

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	

Trial information

Trial identification

Sponsor protocol code	RG_14-144

Additional study identifiers

ISRCTN number	ISRCTN22287432
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmngham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TT
Public contact	Bubble Trial coordinator, CRCTU bubble@trials.bham.ac.uk, Cancer Research UK Clinical Trials Unit (CRCTU), +44 01213717862, bubble@trials.bham.ac.uk
Scientific contact	Bubble Trial coordinator, CRCTU bubble@trials.bham.ac.uk, CRCTU, University of Birmingham, Edgbaston, Birmingham, UK, B15 2TT, +44 01213717862, bubble@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	29 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 April 2020
Global end of trial reached?	Yes
Global end of trial date	09 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the maximum tolerated dose of buparlisib and bortezomib in combination (dose escalation part)

To evaluate the safety of the combination of buparlisib and bortezomib in patients with relapsed/refractory MM (dose expansion part)

Protection of trial subjects:

Specific dose modifications were recommended to decrease the incidence and relieve the symptoms of:
For Bortezomib:
peripheral neuropathy, autonomic neuropathy, thrombocytopenia, neutrocytopenia

For Buparsilib:
thrombocytopenia, neutrocytopenia
renal and hepatic toxicities,
hyperglycaemia,
cardiac toxicities: LV systolic dysfunction, QTc prolongation,
rash and skin toxicity,
fatigue,
pneumonitis,
stomatitis/oral mucositis,
diarrhoea,
pyschiatric disorders/mood alterations

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	23 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	5
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	2
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

5 patients were recruited between July 2016 and July 2017. These patients were recruited from 4 of a possible 13 haemato-oncology centres in the UK.

Pre-assignment

Screening details:

Screening commenced following consent and prior to patient registration in order to confirm eligibility. Screening assessments included: Medical history, weight, demographic data, blood tests, clinical and cardiac assessments, ECOG assessments, assessment of constitutional symptoms, urinalysis, bone marrow biopsy, pregnancy test and CT/MRI/PET scan

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	Buparlisib and Bortezomib

Arm description:

Experimental arm

Arm type	Experimental
Investigational medicinal product name	Buparlisib
Investigational medicinal product code	
Other name	BKM120
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

60mg tablet, once daily for 28 days.

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Calculated based on the patient's BMA; 1.0mg/m2.

Number of subjects in period 1	Buparlisib and Bortezomib
Started	5
Completed	0
Not completed	5
Withdrew from trial	1
Toxicity	1
Disease progression	3

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	5	5	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2	2	
From 65-84 years	3	3	
85 years and over	0	0	
Age continuous Units: years			
median	71		
full range (min-max)	60 to 74	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	1	1	
Prior lines of treatment Units: Subjects			
RD/RCD, VAD/CVAD, ASCT	1	1	
TD/CTD, VD/VCD, VAD/CVAD, ASCT	1	1	
TD/CTD, ASCT	1	1	
TD/CTD, RD/RCD, VD/VCD, MP, ASCT	1	1	
TD/CTD, RD/RCD, VD/VCD, ASCT	1	1	
ISS Stage Units: Subjects			
Stage I	1	1	
Stage II	2	2	
Stage III	2	2	
Paraprotein Type Units: Subjects			
IgG	4	4	
IgA	1	1	
Light chain type Units: Subjects			
Kappa	3	3	
Lambda	2	2	

serum paraprotein levels Units: g/L arithmetic mean full range (min-max)	 29.52 14.50 to 47.30	 -	
Haematocrit Units: L/L arithmetic mean full range (min-max)	 .30 .26 to .35	 -	
Haemoglobin Units: g/L arithmetic mean full range (min-max)	 100.80 83.00 to 117.00	 -	
Lymphocytes Units: 10^ 9/L arithmetic mean full range (min-max)	 1.22 0.90 to 1.50	 -	
Neutrophils Units: 10^9/L arithmetic mean full range (min-max)	 3.04 1.80 to 5.30	 -	
Platelets Units: 10^9 /L arithmetic mean full range (min-max)	 150.60 93.00 to 272.00	 -	
White blood cell count Units: 10^9 /L arithmetic mean full range (min-max)	 4.92 3.80 to 7.20	 -	
Albumin			
Albumin			
Units: g/L arithmetic mean full range (min-max)	 32.80 29.00 to 39.00	 -	
ALP			
ALP			
Units: U/L arithmetic mean full range (min-max)	 76.60 58.00 to 108.00	 -	
ALT			
ALT			
Units: U/L arithmetic mean full range (min-max)	 14.20 2.00 to 20.00	 -	
AST			
AST			
Units: U/L arithmetic mean full range (min-max)	 31.40 15.00 to 65.00	 -	
Bilirubin			
Bilirubin			
Units: micromole(s)/litre arithmetic mean	 11.60		

full range (min-max)	7.00 to 20.00	-	
Calcium			
Calcium			
Units: mmol/L			
arithmetic mean	2.15		
full range (min-max)	2.03 to 2.27	-	
Chloride			
Chloride			
Units: mmol/L			
arithmetic mean	106.00		
full range (min-max)	103.00 to 109.00	-	
Creatinine			
Creatinine			
Units: micromole(s)/litre			
arithmetic mean	80.40		
full range (min-max)	64.00 to 123.00	-	
C-Reactive protein			
C-Reactive Protein			
Units: mg/L			
arithmetic mean	13.60		
full range (min-max)	1.00 to 39.00	-	
eGFR			
eGFR			
Units: ml/min			
arithmetic mean	72.80		
full range (min-max)	39.00 to 90.00	-	
HbA1C			
HbA1C			
Units: percentage			
arithmetic mean	33.66		
full range (min-max)	5.30 to 48.00	-	
LDH			
LDH			
Units: U/L			
arithmetic mean	242.60		
full range (min-max)	181.00 to 357.00	-	
Lipase			
Lipase			
Units: U/L			
arithmetic mean	32.50		
full range (min-max)	19.00 to 49.00	-	
Phosphate			
Phosphate			
Units: mmol/L			
arithmetic mean	0.95		
full range (min-max)	0.80 to 1.20	-	
Potassium			
Potassium			
Units: mmol/L			
arithmetic mean	4.00		
full range (min-max)	3.70 to 4.60	-	
Sodium			

Sodium			
Units: millimole(s)/litre			
arithmetic mean	140.40		
full range (min-max)	135.00 to 146.00	-	
Total Bilirubin			
Total bilirubin			
Units: micromole(s)/litre			
arithmetic mean	12.00		
full range (min-max)	7.00 to 20.00	-	
Urea			
Urea			
Units: millimole(s)/litre			
arithmetic mean	5.60		
full range (min-max)	3.50 to 7.50	-	
Uric acid			
Uric acid			
Units: millimole(s)/litre			
arithmetic mean	343.40		
full range (min-max)	207.00 to 527.00	-	
Magnesium			
Magnesium			
Units: mmol/L			
arithmetic mean	2.80		
full range (min-max)	1.00 to 4.00	-	

End points

End points reporting groups

Reporting group title	Buparlisib and Bortezomib
Reporting group description:	
Experimental arm	

Primary: Incidence of DLTs

End point title	Incidence of DLTs[1]
End point description:	
Number of DLTs in the dose escalation phase.	
End point type	Primary
End point timeframe:	
Dose escalation phase only.	

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: This end point is just a count of the number of DLTs, therefore no statistics are appropriate.

End point values	Buparlisib and Bortezomib			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: number of DLTs	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were reported from the date of commencement of protocol defined treatment until 30 days after the administration of treatment.

Adverse event reporting additional description:

Adverse Events (AEs) were reported on an AE form and returned to the Trials Office. AE's were reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4. SAE forms were faxed to the Trials Office; seriousness and causality were determined independently by a Clinical Coordinator.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Treated patients

Reporting group description:

All 5 patients who received Buparlisib and Bortezomib

Serious adverse events	Treated patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Postural hypotension			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Lung infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to	0 / 1		

treatment / all			
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Treated patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
Vascular disorders			
Postural hypertension			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Injection site reaction			
subjects affected / exposed	4 / 5 (80.00%)		
occurrences (all)	4		
Non cardiac chest pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Fever			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Coryzal symptoms			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Psychiatric disorders			
Low in mood			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Delusions			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Anxiety			

subjects affected / exposed occurrences (all) Feeing introspective, mood changes subjects affected / exposed occurrences (all) Mood changes, feeling emotional subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Injury, poisoning and procedural complications Bruising subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Investigations Platelet count decreased subjects affected / exposed occurrences (all) Creatinine increased subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all) alanine transferase levels increased subjects affected / exposed occurrences (all) Lymphocyte count decreased subjects affected / exposed occurrences (all)	 3 / 5 (60.00%) 20 1 / 5 (20.00%) 1 1 / 5 (20.00%) 5 1 / 5 (20.00%) 2 1 / 5 (20.00%) 1 1 / 5 (20.00%) 3		
Cardiac disorders Atrial fibrillation alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		

Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 2 / 5 (40.00%) 9		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	 2 / 5 (40.00%) 2 1 / 5 (20.00%) 1		
Nervous system disorders Peripheral sensory neuropathy subjects affected / exposed occurrences (all) Memory impairment subjects affected / exposed occurrences (all) Muzziness of brain subjects affected / exposed occurrences (all) Light headedness subjects affected / exposed occurrences (all) Headache alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 2 / 5 (40.00%) 2 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Eye disorders Dry Eye subjects affected / exposed occurrences (all) Increased ocular pressure subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Bloating subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) reflux oesophagitis subjects affected / exposed occurrences (all) intermittent loose stool subjects affected / exposed occurrences (all) GI symptoms subjects affected / exposed occurrences (all)	 4 / 5 (80.00%) 5 1 / 5 (20.00%) 1 2 / 5 (40.00%) 2 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Rib pain subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		

Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Infections and infestations			
Site infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Sepsis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Lower respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2015	SA 1: Substantial amendment for ethical approval. Change to amend from requiring contraception for 8 weeks to requiring contraception for 3 months/ 12 weeks as specified by the SmPC for Bortezomib.
18 August 2016	SA 2: Substantial amendment to add guidelines for the management of pancreatitis, to update the safety information relating to buparlisib and to add severe hypersensitivity reactions as a reason for discontinuing study drug therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 November 2017	Recruitment to the trial was stopped due to insufficient supply of the study drug Buparsilib, as Novartis had informed us in Jan 2017 that it would be halting production of the drug due to a negative risk/benefit assessment in 2 breast cancer studies.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Early termination of the study due to the halt in production and supply of one of the study drugs, Buparlisib, resulted in only 5 patients on the study, with none of them completing their treatment, and no analysis of the data could be performed.

Notes: