Clinical trial results:
An open-label Phase II study of BKM120 in subjects with relapsed and refractory
diffuse large B-cell lymphoma, mantle cell lymphoma and follicular lymphoma

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Summary

EudraCT number	2012-002208-41
Trial protocol	DE IT ES BE
Global end of trial date	20 July 2017
Results information	
Result version number	v1 (current)
This version publication date	04 August 2018
First version publication date	04 August 2018

Trial information

Trial identification	
Sponsor protocol code	CBKM120Z2402
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01693614
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the efficacy of buparlisib in subjects with relapsed/refractory Non-Hodgkin Lymphoma (NHL) in the three different histological subgroups (cohorts).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 February 2013
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	Belgium: 4
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	72
EEA total number of subjects	33

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)	34
From 65 to 84 years	37
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Seventy-two patients were enrolled in the study and received treatment. Primary reason for not completing is presented

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	DLBCL Cohort

Arm description:

Diffuse large B-cell lymphoma cohort

Arm type	Experimental
Investigational medicinal product name	buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100 mg was administered orally once daily on a continuous dosing schedule for 28 days (treatment cycle)

Arm title	MCL Cohort

Arm description:

Mantle cell lymphoma cohort

Arm type	Experimental
Investigational medicinal product name	buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100 mg was administered orally once daily on a continuous dosing schedule for 28 days (treatment cycle)

Arm title	FL Cohort

Arm description:

Follicular lymphoma cohort

Arm type	Experimental
Investigational medicinal product name	buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100 mg was administered orally once daily on a continuous dosing schedule for 28 days (treatment cycle)

Number of subjects in period 1	DLBCL Cohort	MCL Cohort	FL Cohort
Started	26	22	24
Completed	0	0	0
Not completed	26	22	24
Adverse event, serious fatal	1	-	-
Physician decision	1	1	4
Consent withdrawn by subject	1	-	7
Disease progression	11	8	7
Adverse event, non-fatal	7	11	5
Protocol deviation	5	2	1

Baseline characteristics

Reporting groups	
Reporting group title	DLBCL Cohort
Reporting group description: Diffuse large B-cell lymphoma cohort	
Reporting group title	MCL Cohort
Reporting group description: Mantle cell lymphoma cohort	
Reporting group title	FL Cohort
Reporting group description: Follicular lymphoma cohort	

Reporting group values	DLBCL Cohort	MCL Cohort	FL Cohort
Number of subjects	26	22	24
Age categorical Units: Subjects			
Adults (18-64 years)	13	8	13
From 65-84 years	13	14	10
85 years and over	0	0	1
Age Continuous Units: years			
arithmetic mean	60.0	67.9	61.4
standard deviation	± 14.57	± 8.56	± 13.11
Sex: Female, Male Units: Subjects			
Female	8	4	11
Male	18	18	13
Race/Ethnicity, Customized Units: Subjects			
Caucasian|	19	17	21
Black|	0	0	1
Asian|	3	2	2
Other|	4	3	0

Reporting group values	Total		
Number of subjects	72		
Age categorical Units: Subjects			
Adults (18-64 years)	34		
From 65-84 years	37		
85 years and over	1		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		

Sex: Female, Male Units: Subjects			
Female	23		
Male	49		
Race/Ethnicity, Customized Units: Subjects			
Caucasian|	57		
Black|	1		
Asian|	7		
Other|	7		

End points

End points reporting groups

Reporting group title	DLBCL Cohort
Reporting group description: Diffuse large B-cell lymphoma cohort	
Reporting group title	MCL Cohort
Reporting group description: Mantle cell lymphoma cohort	
Reporting group title	FL Cohort
Reporting group description: Follicular lymphoma cohort	

Primary: Overall Response Rate (ORR) per investigator at 6 months (FAS)

End point title	Overall Response Rate (ORR) per investigator at 6 months (FAS)[1]

End point description:

Overall Response rate is the number of patients in a cohort who experience either complete response (CR) or partial response (PR) during their follow-up after treatment start divided by the total number of patients included in the corresponding cohort according to Cheson criteria The analysis for each cohort was based on an exact binomial test comparing the ORR to the reference level of 10% (null hypothesis) in the FAS. The test for each cohort used a significance level of 5%. The ORR was presented together with an exact 95% Clopper- Pearson confidence interval. Disease Control Rate (DCR) is the number of patients with CR, PR or SD (stable disease). Patients for whom the best response after treatment start was missing, unknown (UNK) or progressive disease (PD) were considered non-responders and were counted in the denominator for the estimation of the ORR

End point type	Primary

End point timeframe:

Baseline up to 6 months

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: Analysis described in Primary Outcome description

End point values	DLBCL Cohort	MCL Cohort	FL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	22	24	
Units: percentage of participants				
number (confidence interval 95%)				
ORR (3,5,6)|	11.5 (2.45 to 30.15)	22.7 (7.82 to 45.37)	25.0 (9.77 to 46.71)	
DCR (n=8,18,21)|	30.8 (14.33 to 51.79)	81.8 (59.72 to 94.81)	87.5 (67.64 to 97.34)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with responses at 6 months (FAS)

End point title	Percentage of participants with responses at 6 months (FAS)[2]

End point description:

Complete Response (CR) = complete disappearance of all index extranodal lesions, Partial Response (PR) = At least 50% decrease from baseline in the SPD restricted to all index extranodal lesions, Stable Disease (SD) = Failure to attain the criteria needed for CR or PR and failure to fulfill the criteria for PD, Progressive Disease (PD) = At least a 50% increase from nadir2 in the SPD restricted to all index extranodal lesions. Nadir is defined as the smallest sum of the product of the diameters restricted to all index extranodal lesions recorded so far, at or after baseline. At each assessment, response will be first assessed for meeting CR status. If CR status is not met, response will be assessed for PD status, then PR status and SD status.

End point type	Primary

End point timeframe:

Baseline up to approximately 6 months

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: Analysis described in Primary Outcome description

End point values	DLBCL Cohort	MCL Cohort	FL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	22	24	
Units: percentage of participants				
number (not applicable)				
CR (1,1,0)|	3.8	4.5	0	
PR (n=2,4,6)|	7.7	18.2	25.0	
SD (n=5,13,15)|	19.2	59.1	62.5	
PD (n=12,2,1)|	46.2	9.1	4.2	
Unknown (n=6,2,2)|	23.1	9.1	8.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression- Free Survival (PFS) based on investigator assessment (FAS)

End point title	Progression- Free Survival (PFS) based on investigator assessment (FAS)

End point description:

Progression-free survival (PFS) is the time from the date of treatment start to the date of the first documented progressive disease (PD) or death due to any cause using Kaplan-Meier method by cohort.

End point type	Secondary

End point timeframe:

Baseline up to approximately 18 months

End point values	DLBCL Cohort	MCL Cohort	FL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	22	24	
Units: months				
median (confidence interval 95%)	1.8 (1.51 to 4.01)	11.3 (3.81 to 38.90)	9.1 (3.75 to 14.46)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response for diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (FL) cohorts (FAS)

End point title	Duration of response for diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (FL) cohorts (FAS)[3]

End point description:

Duration of response is the time from the date of first occurrence of complete response (CR) or partial response (PR) to the date of the first documented progressive disease (PD) or death due to any cause.

End point type	Secondary

End point timeframe:

Baseline up to approximately 18 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only two cohorts met the criteria of duration of response.

End point values	DLBCL Cohort	FL Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	6		
Units: weeks				
median (confidence interval 95%)	2.2 (1.15 to 9.99)	11 (3.94 to 99.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (FAS)

End point title	Overall survival (FAS)

End point description:

Overall survival (OS) is the time from treatment start to the date of death due to any cause

End point type	Secondary

End point timeframe:

Baseline up to approximately 18 months

End point values	DLBCL Cohort	MCL Cohort	FL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	22	24	
Units: events				
number (not applicable)				
OS events (n=13,5,2)|	50.0	22.7	8.3	
Number censored (n=13,17,22)|	50.0	77.3	91.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival- Median (FAS)

End point title	Overall survival- Median (FAS)

End point description:

Overall survival (OS) is the time from treatment start to the date of death due to any cause. Estimates done by cohort using Kaplan-Meier method with 95%
confidence intervals. 999 values = not estimable

End point type	Secondary

End point timeframe:

Baseline up to approximately 18 months

End point values	DLBCL Cohort	MCL Cohort	FL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	22	24	
Units: months				
median (confidence interval 95%)	5.2 (3.06 to 9.9)	99.99 (15.64 to 99.99)	99.99 (22.74 to 99.99)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit up to approximately 18 months

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	DLBCL Cohort
Reporting group description:	
DLBCL	
Reporting group title	FL Cohort
Reporting group description:	
FL	
Reporting group title	MCL Cohort
Reporting group description:	
MCL	

Serious adverse events	DLBCL Cohort	FL Cohort	MCL Cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 26 (46.15%)	7 / 24 (29.17%)	12 / 22 (54.55%)
number of deaths (all causes)	7	0	1
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Gait disturbance			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 26 (0.00%)	2 / 24 (8.33%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory failure			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract congestion			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	2 / 22 (9.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric decompensation			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebellar infarction			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			

subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Essential tremor			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 26 (3.85%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Nausea			

subjects affected / exposed	2 / 26 (7.69%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctalgia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 26 (7.69%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Toxic skin eruption			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendonitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lung infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Meningitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	2 / 22 (9.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia streptococcal			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	DLBCL Cohort	FL Cohort	MCL Cohort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 26 (96.15%)	23 / 24 (95.83%)	22 / 22 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	2 / 26 (7.69%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	4 / 22 (18.18%)
occurrences (all)	0	0	4
Jugular vein thrombosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 26 (11.54%)	4 / 24 (16.67%)	5 / 22 (22.73%)
occurrences (all)	4	4	6
Face oedema			
subjects affected / exposed	0 / 26 (0.00%)	2 / 24 (8.33%)	0 / 22 (0.00%)
occurrences (all)	0	3	0
Fatigue			
subjects affected / exposed	6 / 26 (23.08%)	13 / 24 (54.17%)	8 / 22 (36.36%)
occurrences (all)	7	27	11
Oedema peripheral			
subjects affected / exposed	0 / 26 (0.00%)	3 / 24 (12.50%)	0 / 22 (0.00%)
occurrences (all)	0	4	0
Pyrexia			

subjects affected / exposed	3 / 26 (11.54%)	1 / 24 (4.17%)	2 / 22 (9.09%)
occurrences (all)	4	2	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 26 (7.69%)	4 / 24 (16.67%)	4 / 22 (18.18%)
occurrences (all)	2	4	4
Dyspnoea			
subjects affected / exposed	2 / 26 (7.69%)	2 / 24 (8.33%)	2 / 22 (9.09%)
occurrences (all)	2	3	3
Pleural effusion			
subjects affected / exposed	0 / 26 (0.00%)	2 / 24 (8.33%)	1 / 22 (4.55%)
occurrences (all)	0	2	1
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 26 (3.85%)	1 / 24 (4.17%)	3 / 22 (13.64%)
occurrences (all)	1	1	3
Anxiety			
subjects affected / exposed	6 / 26 (23.08%)	5 / 24 (20.83%)	7 / 22 (31.82%)
occurrences (all)	6	7	11
Confusional state			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	2 / 22 (9.09%)
occurrences (all)	0	1	2
Depression			
subjects affected / exposed	8 / 26 (30.77%)	6 / 24 (25.00%)	7 / 22 (31.82%)
occurrences (all)	8	9	8
Insomnia			
subjects affected / exposed	2 / 26 (7.69%)	1 / 24 (4.17%)	2 / 22 (9.09%)
occurrences (all)	2	1	2
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 26 (7.69%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	2	1	0
Weight decreased			
subjects affected / exposed	3 / 26 (11.54%)	4 / 24 (16.67%)	8 / 22 (36.36%)
occurrences (all)	3	5	8
Nervous system disorders			

Dizziness			
subjects affected / exposed	1 / 26 (3.85%)	2 / 24 (8.33%)	1 / 22 (4.55%)
occurrences (all)	1	2	1
Dysgeusia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 24 (8.33%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Headache			
subjects affected / exposed	0 / 26 (0.00%)	5 / 24 (20.83%)	1 / 22 (4.55%)
occurrences (all)	0	5	1
Memory impairment			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	2 / 22 (9.09%)
occurrences (all)	0	1	2
Neuropathy peripheral			
subjects affected / exposed	0 / 26 (0.00%)	1 / 24 (4.17%)	2 / 22 (9.09%)
occurrences (all)	0	1	2
Tremor			
subjects affected / exposed	1 / 26 (3.85%)	2 / 24 (8.33%)	4 / 22 (18.18%)
occurrences (all)	1	3	7
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 26 (3.85%)	2 / 24 (8.33%)	3 / 22 (13.64%)
occurrences (all)	1	3	3
Leukopenia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	2 / 22 (9.09%)
occurrences (all)	1	0	2
Neutropenia			
subjects affected / exposed	2 / 26 (7.69%)	1 / 24 (4.17%)	1 / 22 (4.55%)
occurrences (all)	4	1	1
Thrombocytopenia			
subjects affected / exposed	1 / 26 (3.85%)	2 / 24 (8.33%)	1 / 22 (4.55%)
occurrences (all)	1	2	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 26 (0.00%)	2 / 24 (8.33%)	3 / 22 (13.64%)
occurrences (all)	0	3	3
Eye disorders			

Cataract			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	3
Dry eye			
subjects affected / exposed	0 / 26 (0.00%)	2 / 24 (8.33%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Vision blurred			
subjects affected / exposed	0 / 26 (0.00%)	2 / 24 (8.33%)	1 / 22 (4.55%)
occurrences (all)	0	2	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 26 (15.38%)	1 / 24 (4.17%)	3 / 22 (13.64%)
occurrences (all)	4	1	3
Constipation			
subjects affected / exposed	3 / 26 (11.54%)	3 / 24 (12.50%)	5 / 22 (22.73%)
occurrences (all)	3	3	5
Diarrhoea			
subjects affected / exposed	5 / 26 (19.23%)	9 / 24 (37.50%)	6 / 22 (27.27%)
occurrences (all)	10	12	8
Dyspepsia			
subjects affected / exposed	2 / 26 (7.69%)	4 / 24 (16.67%)	2 / 22 (9.09%)
occurrences (all)	3	5	3
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 26 (0.00%)	2 / 24 (8.33%)	1 / 22 (4.55%)
occurrences (all)	0	3	1
Nausea			
subjects affected / exposed	8 / 26 (30.77%)	10 / 24 (41.67%)	6 / 22 (27.27%)
occurrences (all)	8	17	6
Vomiting			
subjects affected / exposed	3 / 26 (11.54%)	3 / 24 (12.50%)	0 / 22 (0.00%)
occurrences (all)	5	3	0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			

Dry skin			
subjects affected / exposed	0 / 26 (0.00%)	3 / 24 (12.50%)	1 / 22 (4.55%)
occurrences (all)	0	3	1
Pruritus			
subjects affected / exposed	2 / 26 (7.69%)	3 / 24 (12.50%)	3 / 22 (13.64%)
occurrences (all)	2	3	3
Rash			
subjects affected / exposed	2 / 26 (7.69%)	4 / 24 (16.67%)	3 / 22 (13.64%)
occurrences (all)	2	9	3
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 26 (0.00%)	3 / 24 (12.50%)	2 / 22 (9.09%)
occurrences (all)	0	3	2
Muscle spasms			
subjects affected / exposed	0 / 26 (0.00%)	3 / 24 (12.50%)	2 / 22 (9.09%)
occurrences (all)	0	4	2
Myalgia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 24 (8.33%)	0 / 22 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 24 (0.00%)	2 / 22 (9.09%)
occurrences (all)	1	0	2
Herpes zoster			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Pneumonia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 24 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Urinary tract infection			
subjects affected / exposed	2 / 26 (7.69%)	3 / 24 (12.50%)	1 / 22 (4.55%)
occurrences (all)	2	5	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 26 (7.69%)	7 / 24 (29.17%)	7 / 22 (31.82%)
occurrences (all)	2	8	7

Diabetes mellitus			
subjects affected / exposed	0 / 26 (0.00%)	2 / 24 (8.33%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Hyperglycaemia			
subjects affected / exposed	10 / 26 (38.46%)	6 / 24 (25.00%)	10 / 22 (45.45%)
occurrences (all)	13	8	15
Hypokalaemia			
subjects affected / exposed	3 / 26 (11.54%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	3	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 October 2012	The primary purpose for amending the protocol was to include monitoring for evidence of tumor lysis syndrome (TLS) during treatment with buparlisib. TLS might occur during treatment for diffuse large B-cell lymphoma; therefore the protocol and visit schedule were amended to include appropriate monitoring for evidence of TLS during the first 72 hours of study treatment. The requirement for not allowing previous treatment with mTOR inhibitors was removed from the exclusion criteria. Removing this exclusion broadened eligibility for this population that has a significant unmet medical need and potentially no anticipated impact on study results.
10 January 2014	The main purpose of this amendment was to update and align the management of selected AEs across the buparlisib program and with the Investigator's Brochure version 6, specifically psychiatric disorders, hyperglycemia grade 2, skin rash and stomatitis. In addition to account for over enrollment, the number of subjects to be enrolled was capped to N=28 for all three cohorts.
05 August 2015	The main purpose of this protocol amendment was to provide additional guidance to Investigators around management of liver toxicities.
09 August 2016	The main purpose of this protocol amendment was to provide a clarification on the measures to follow when a subject exhibited suicidal ideation regardless of the response to question 9 of the PHQ-9 questionnaire. Patient Health Questionnaire-9 (PHQ-9) was used to increase the sensitivity of identifying potential depression and suicidal thoughts.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: