Clinical trial results:
A Phase 2, Open-label Study of Zanubrutinib (BGB-3111) in Patients with Relapsed or Refractory Marginal Zone Lymphoma

Summary

EudraCT number	2018-001284-24
Trial protocol	GB FR IT
Global end of trial date	04 May 2022

Results information

Result version number	v1 (current)
This version publication date	19 May 2023
First version publication date	19 May 2023

Trial information

Trial identification

Sponsor protocol code	BGB-3111-214

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03846427
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BeiGene, Ltd., c/o BeiGene USA, Inc.
Sponsor organisation address	1840 Gateway Drive, Third Floor, San Mateo, United States, 94404
Public contact	BeiGene Clinical Support, BeiGene, Ltd., 1 877-828-5568, clinicaltrials@beigene.com
Scientific contact	BeiGene Clinical Support, BeiGene, Ltd., 1 877-828-5568, clinicaltrials@beigene.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 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 May 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of zanubrutinib in relapsed or refractory marginal zone lymphoma as measured by overall response rate in accordance with the Lugano Classification determined by independent central review.

Protection of trial subjects:

This trial was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of GCP as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki. The IEC/IRB-approved ICF was signed and dated by the subject or the subject's legally authorized representative before his or her participation in the study. A copy of each signed ICF was provided to the subject or the subject's legally authorized representative. All signed and dated ICFs were retained in each patient's study file or in the site file. For any updated or revised ICFs, written informed consent was obtained using the IEC/IRB-approved updated/revised ICFs for continued participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 February 2019
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: 11
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	China: 11
Country: Number of subjects enrolled	New Zealand: 7
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Korea, Republic of: 1
Worldwide total number of subjects	68
EEA total number of subjects	17

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)	27
From 65 to 84 years	38
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 31 study centers in 9 countries. A total of 38 participants rolled over to BGB-3111-LTE1 (NCT04170283) after study completion.

Pre-assignment

Screening details:

The study was composed of an initial screening phase (up to 35 days), a single-arm treatment phase, and a follow-up phase.

Period 1

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

Arms

Arm title	Zanubrutinib

Arm description:

Zanubrutinib 160 mg (two 80-mg capsules) orally twice daily with or without food until progressive disease, intolerable toxicity, or withdrawal of consent

Arm type	Experimental
Investigational medicinal product name	Zanubrutinib
Investigational medicinal product code	
Other name	BGB-3111, Brukinsa
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Zanubrutinib 160 mg (two 80-mg capsules) orally twice daily with or without food

Number of subjects in period 1	Zanubrutinib
Started	68
Completed	51
Not completed	17
Consent withdrawn by subject	3
Physician decision	1
Death	13

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	68	68	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	67.9		
standard deviation	± 11.41	-	
Gender categorical Units: Subjects			
Female	32	32	
Male	36	36	
Race/Ethnicity Units: Subjects			
Asian	13	13	
White	40	40	
Multiple	2	2	
Other	1	1	
Unknown	1	1	
Not Reported	11	11	

End points

End points reporting groups

Reporting group title	Zanubrutinib

Reporting group description:

Zanubrutinib 160 mg (two 80-mg capsules) orally twice daily with or without food until progressive disease, intolerable toxicity, or withdrawal of consent

Primary: Overall Response Rate (ORR) by Independent Review Committee (IRC) Assessment

End point title	Overall Response Rate (ORR) by Independent Review Committee (IRC) Assessment[1]

End point description:

ORR is defined as the percentage of subjects with complete or partial response as the best overall response, as determined by an IRC using the Lugano Classification

End point type	Primary

End point timeframe:

Up to approximately 3 years and 2.5 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: Single-arm study: superiority test, P<0.0001; P value was based on the exact binomial test against the null hypothesis of ORR = 30% with alternative of ORR > 30%

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Percentage of subjects				
number (confidence interval 95%)	68.2 (55.56 to 79.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR by Investigator Assessment

End point title	ORR by Investigator Assessment

End point description:

ORR is defined as the percentage of subjects with complete or partial response as the best overall response, as determined by the investigator using the Lugano Classification.

End point type	Secondary

End point timeframe:

Up to approximately 3 years and 2.5 months

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Percentage of subjects				
number (confidence interval 95%)	75.8 (63.64 to 85.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR by IRC Assessment Using Positron Emission Tomography-Computed Tomography (PET-CT)

End point title	ORR by IRC Assessment Using Positron Emission Tomography-Computed Tomography (PET-CT)

End point description:

ORR is defined as the percentage of subjects with complete and partial response as the best overall response, as determined by an IRC using PET-CT assessment data for subjects with fluorodeoxyglucose (FDG)-avid disease; analysis set consisted of evaluable subjects with FDG-avid disease at baseline

End point type	Secondary

End point timeframe:

Up to approximately 3 years and 2.5 months

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: Percentage of subjects				
number (confidence interval 95%)	69.5 (56.13 to 80.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) by Investigator Assessment

End point title	Progression-free Survival (PFS) by Investigator Assessment

End point description:

PFS is defined as the time from first dose until first documentation of progression or death, whichever comes first, as assessed by the investigator using Lugano Classification

End point type	Secondary

End point timeframe:

Up to approximately 3 years and 2.5 months

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	66[2]			
Units: Months				
median (full range (min-max))	9999 (16.5 to 9999)			

Notes:

[2] - 9999 = Not estimable due to insufficient number of subjects with events

Statistical analyses

No statistical analyses for this end point

Secondary: PFS Event-Free Rate by Investigator Assessment

End point title	PFS Event-Free Rate by Investigator Assessment

End point description:

PFS is defined as the time from first dose until first documentation of progression or death, whichever comes first, as assessed by the investigator using Lugano Classification. The Kaplan-Meier method was used to estimate the percentage of subjects who were event-free for PFS at 24 months with 95% confidence intervals estimated using Greenwood’s formula.

End point type	Secondary

End point timeframe:

Up to 3 years and 2.5 months after first participant enrolled; Month 24 reported

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Percentage of subjects				
number (confidence interval 95%)	57.9 (44.83 to 68.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS by IRC Assessment

End point title	PFS by IRC Assessment

End point description:

PFS is defined as the time from first dose until first documentation of progression or death, whichever comes first, as assessed by an IRC using Lugano Classification

End point type	Secondary

End point timeframe:

Up to approximately 3 years and 2.5 months

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	66[3]			
Units: Months				
median (full range (min-max))	9999 (27.6 to 9999)			

Notes:

[3] - 9999 = Not estimable due to insufficient number of subjects with events

Statistical analyses

No statistical analyses for this end point

Secondary: PFS Event-Free Rate by IRC Assessment

End point title	PFS Event-Free Rate by IRC Assessment

End point description:

PFS is defined as the time from first dose until first documentation of progression or death, whichever comes first, as assessed by the IRC using Lugano Classification. The Kaplan-Meier method was used to estimate the percentage of subjects who were event-free for PFS at 24 months with 95% confidence intervals estimated using Greenwood's formula.

End point type	Secondary

End point timeframe:

Up to 3 years and 2.5 months after first participant enrolled; Month 24 reported

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Percentage of subjects				
number (confidence interval 95%)	70.9 (57.20 to 80.95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from first study drug administration to the date of death due to any cause

End point type	Secondary

End point timeframe:

Up to approximately 3 years and 2.5 months

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	66[4]			
Units: Months				
median (full range (min-max))	9999 (9999 to 9999)			

Notes:

[4] - 9999 = Not estimable due to insufficient number of subjects with events

Statistical analyses

No statistical analyses for this end point

Secondary: OS Event-Free Rate

End point title	OS Event-Free Rate

End point description:

OS is defined as the time from first study drug administration to the date of death due to any cause. The Kaplan-Meier method was used to estimate the percentage of subjects who were event-free for OS at 24 months with 95% confidence intervals estimated using Greenwood's formula.

End point type	Secondary

End point timeframe:

Up to 3 years and 2.5 months after first participant enrolled; Month 24 reported

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Percentage of subjects				
number (confidence interval 95%)	85.9 (74.7 to 92.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) by Investigator Assessment

End point title	Duration of Response (DOR) by Investigator Assessment

End point description:

DOR is defined as the time from the date that response criteria are first met to the date that progressive disease is objectively documented or death, whichever comes first, as assessed by the investigator using Lugano Classification; DOR was summarized for responders only, defined as subjects with a best overall response of partial response or above

End point type	Secondary

End point timeframe:

Up to approximately 3 years and 2.5 months

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	50[5]			
Units: Months				
median (full range (min-max))	9999 (22.1 to 9999)			

Notes:

[5] - 9999 = Not estimable due to insufficient number of subjects with events

Statistical analyses

No statistical analyses for this end point

Secondary: DOR Event-Free Rate by Investigator Assessment

End point title	DOR Event-Free Rate by Investigator Assessment

End point description:

DOR is defined as the time from the date that response criteria are first met to the date that progressive disease is objectively documented or death, whichever comes first, as assessed by the investigator using Lugano Classification. The Kaplan-Meier method was used to estimate the percentage of subjects who were event-free for progression or death at 24 months with 95% confidence intervals estimated using Greenwood's formula; DOR was summarized for responders only, defined as subjects with a best overall response of partial response or above.

End point type	Secondary

End point timeframe:

Up to 3 years and 2.5 months after first participant enrolled; Month 24 reported

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Percentage of subjects				
number (confidence interval 95%)	60.8 (44.8 to 73.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: DOR by IRC Assessment

End point title	DOR by IRC Assessment

End point description:

DOR is defined as the time from the date that response criteria are first met to the date that progressive disease is objectively documented or death, whichever comes first, as assessed by the IRC using Lugano Classification; DOR was summarized for responders only, defined as subjects with a best overall response of partial response or above.

End point type	Secondary

End point timeframe:

Up to approximately 3 years and 2.5 months

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	45[6]			
Units: Months				
median (full range (min-max))	9999 (25.0 to 9999)			

Notes:

[6] - 9999 = Not estimable due to insufficient number of subjects with events

Statistical analyses

No statistical analyses for this end point

Secondary: DOR Event-Free Rate by IRC Assessment

End point title	DOR Event-Free Rate by IRC Assessment

End point description:

DOR is defined as the time from the date that response criteria are first met to the date that progressive disease is objectively documented or death, whichever comes first, as assessed by the IRC using Lugano Classification. The Kaplan-Meier method was used to estimate the percentage of subjects who were event-free for progression or death at 24 months with 95% confidence intervals estimated using Greenwood's formula; DOR was summarized for responders only, defined as subjects with a best overall response of partial response or above.

End point type	Secondary

End point timeframe:

At Month 24

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Percentage of subjects				
number (confidence interval 95%)	72.9 (54.4 to 84.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure (TTF)

End point title	Time to Treatment Failure (TTF)

End point description:

TTF is defined as the time from study treatment start to the date of discontinuation of study drug due to any reason

End point type	Secondary

End point timeframe:

Up to approximately 3 years and 2.5 months

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	66[7]			
Units: Months				
median (full range (min-max))	27.8 (14.7 to 9999)			

Notes:

[7] - 9999 = Not estimable due to insufficient number of subjects with events

Statistical analyses

No statistical analyses for this end point

Secondary: TTF Event-Free Rate

End point title	TTF Event-Free Rate

End point description:

TTF is defined as the time from study treatment start to the date of discontinuation of study drug due to any reason. The Kaplan-Meier method was used to estimate the percentage of subjects who were event-free for TTF at 24 months with 95% confidence intervals estimated using Greenwood’s formula.

End point type	Secondary

End point timeframe:

Up to 3 years and 2.5 months after first participant enrolled; Month 24 reported

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Percentage of subjects				
number (confidence interval 95%)	53.0 (40.4 to 64.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next Line of Therapy

End point title	Time to Next Line of Therapy

End point description:

Time to next line of therapy is defined as the time from study treatment start to the start of the first subsequent therapy for MZL

End point type	Secondary

End point timeframe:

Up to approximately 3 years and 2.5 months

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	66[8]			
Units: Months				
median (full range (min-max))	9999 (9999 to 9999)			

Notes:

[8] - 9999 = Not estimable due to insufficient number of subjects with events

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next Line of Therapy Event-Free Rate

End point title	Time to Next Line of Therapy Event-Free Rate

End point description:

Time to next line of therapy is defined as the time from study treatment start to the start of the first subsequent therapy for MZL. The Kaplan-Meier method was used to estimate the percentage of subjects who were event-free for time to next line of therapy at 24 months with 95% confidence intervals estimated using Greenwood’s formula.

End point type	Secondary

End point timeframe:

Up to 3 years and 2.5 months after first participant enrolled; Month 24 reported

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Percentage of subjects				
number (confidence interval 95%)	74.5 (61.7 to 83.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) by Investigator Assessment

End point title	Time to Response (TTR) by Investigator Assessment

End point description:

TTR is defined as the time from study treatment start to date of the earliest qualifying response (partial response or better) as assessed by the investigator using Lugano Classification; TTR was summarized for responders only, defined as subjects with a best overall response of partial response or above

End point type	Secondary

End point timeframe:

Up to approximately 3 years and 2.5 months

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Months				
median (full range (min-max))	2.79 (1.7 to 16.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: TTR by IRC Assessment

End point title	TTR by IRC Assessment

End point description:

TTR is defined as the time from study treatment start to date of the earliest qualifying response (partial response or better), as assessed by the IRC using Lugano Classification; TTR was summarized for responders only, defined as subjects with a best overall response of partial response or above

End point type	Secondary

End point timeframe:

Up to approximately 3 years and 2.5 months

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Months				
median (full range (min-max))	2.79 (1.7 to 11.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQol 5-dimension 5-level (EQ-5D-5L) Visual Analogue Score (VAS)

End point title	Change From Baseline in EuroQol 5-dimension 5-level (EQ-5D-5L) Visual Analogue Score (VAS)

End point description:

Mean change from baseline in EQ-5D-5L VAS. The EQ-5D-5L measures health outcomes using a VAS to record a subject's self-rated health on a scale from 0 to 100, where 100 is 'the best health you can imagine' and 0 is 'the worst health you can imagine.' Positive change from baseline indicates improved health.

End point type	Secondary

End point timeframe:

Baseline to Cycle 30 (28 days per cycle)

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Cycle 3, n = 57	1.0 (± 18.18)			
Cycle 6, n = 50	2.2 (± 15.78)			
Cycle 9, n = 47	0.2 (± 16.28)			
Cycle 12, n = 42	2.8 (± 16.15)			
Cycle 18, n = 33	5.6 (± 17.68)			
Cycle 24, n = 35	5.8 (± 15.24)			
Cycle 30, n = 28	1.6 (± 18.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Health Status

End point title	Change From Baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Health Status

End point description:

Mean change from baseline in EORTC QLQ-C30 Global Health Status/Quality of Life score. The EORTC QLQ-C30 v3.0 is a questionnaire that assesses quality of life of cancer patients and includes global health status and quality of life questions related to their overall health in which subjects respond based on a 7-point scale, where 1 is very poor and 7 is excellent. Answers are converted to a score of 0 to 100, with a positive score from baseline indicating improved health.

End point type	Secondary

End point timeframe:

Baseline to Cycle 30 (28 days per cycle)

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Cycle 3, n = 58	7.471 (± 19.5396)			
Cycle 6, n = 49	7.823 (± 15.8121)			
Cycle 9, n = 48	5.382 (± 20.0833)			
Cycle 12, n = 42	7.143 (± 17.3216)			
Cycle 18, n = 32	10.677 (± 18.4811)			
Cycle 24, n = 35	9.286 (± 19.2561)			
Cycle 30, n = 28	6.250 (± 20.4910)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events

End point title	Number of Subjects With Adverse Events

End point description:

Number of subjects with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), including laboratory tests, physical exams, and vital signs

End point type	Secondary

End point timeframe:

From first dose to 30 days after last dose of study drug (Up to approximately 3 years and 2.5 months)

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: Subjects				
At least one TEAE	68			
At least one SAE	30			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time 0 to 6 Hours (AUC0-6)

End point title	Area Under the Curve From Time 0 to 6 Hours (AUC0-6)

End point description:

Analysis set included all subjects who had at least 1 postdose zanubrutinib plasma concentration

End point type	Secondary

End point timeframe:

Predose (within 30 min prior to dose) and 0.5, 1, 2, 3, 4, and 6 hours postdose on Cycle 1 Day 1 (28 days per cycle)

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Hour*ng/mL				
arithmetic mean (standard deviation)	868.0 (± 304.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Oral Clearance (CL/F) of Zanubrutinib

End point title	Apparent Oral Clearance (CL/F) of Zanubrutinib

End point description:

Analysis set included all subjects who had at least 1 postdose zanubrutinib plasma concentration

End point type	Secondary

End point timeframe:

Predose (within 30 min prior to dose) and 0.5, 1, 2, 3, 4, and 6 hours postdose on Cycle 1 Day 1 (28 days per cycle)

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Liters/hour				
arithmetic mean (standard deviation)	215.3 (± 114.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax)

End point title	Maximum Observed Concentration (Cmax)

End point description:

End point type	Secondary

End point timeframe:

Predose (within 30 min prior to dose) and 0.5, 1, 2, 3, 4, and 6 hours postdose on Cycle 1 Day 1 (28 days per cycle)

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: nanograms/milliliter				
arithmetic mean (standard deviation)	315.5 (± 120.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half Life (t1/2)

End point title	Elimination Half Life (t1/2)

End point description:

End point type	Secondary

End point timeframe:

Predose (within 30 min prior to dose) and 0.5, 1, 2, 3, 4, and 6 hours postdose on Cycle 1 Day 1 (28 days per cycle)

End point values	Zanubrutinib			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Hours				
median (full range (min-max))	1.2 (0.8 to 2.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose to 30 days after last dose of study drug (Up to approximately 3 years and 2.5 months)

Adverse event reporting additional description:

Defined as an adverse event that had an onset date or worsening in severity from baseline on or after the date of first dose of study drug up to 30 days after study drug discontinuation or initiation of new anticancer therapy, whichever occurred first.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Zanubrutinib

Reporting group description:

Zanubrutinib

Serious adverse events	Zanubrutinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 68 (44.12%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events	5		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Bladder cancer recurrent			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Papillary thyroid cancer			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Organising pneumonia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Platelet count decreased			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acetabulum fracture			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Myocardial infarction			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coronary artery stenosis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Vertebrobasilar insufficiency			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebellar infarction			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 68 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Anaemia				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				
subjects affected / exposed	1 / 68 (1.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				

subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19 pneumonia			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		

Bronchitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Septic encephalopathy			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tuberculosis			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Zanubrutinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 68 (89.71%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	5		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	8 / 68 (11.76%)		
occurrences (all)	13		
Fatigue			
subjects affected / exposed	6 / 68 (8.82%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 68 (10.29%)		
occurrences (all)	8		
Dyspnoea			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		

Epistaxis subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 68 (4.41%) 5 3 / 68 (4.41%) 3		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	3 / 68 (4.41%) 3		
Investigations White blood cell count decreased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 68 (4.41%) 8 3 / 68 (4.41%) 4 4 / 68 (5.88%) 10 5 / 68 (7.35%) 6 3 / 68 (4.41%) 10		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all)	16 / 68 (23.53%) 22 3 / 68 (4.41%) 3		
Nervous system disorders Dizziness			

subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	5		
Lethargy			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	5		
Paraesthesia			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		
Sciatica			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	6 / 68 (8.82%)		
occurrences (all)	11		
Thrombocytopenia			
subjects affected / exposed	7 / 68 (10.29%)		
occurrences (all)	10		
Anaemia			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	15 / 68 (22.06%)		
occurrences (all)	26		
Constipation			
subjects affected / exposed	12 / 68 (17.65%)		
occurrences (all)	15		
Abdominal pain			
subjects affected / exposed	8 / 68 (11.76%)		
occurrences (all)	11		
Vomiting			

subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
Toothache			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	7 / 68 (10.29%)		
occurrences (all)	9		
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	4		
Dysphagia			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 68 (14.71%)		
occurrences (all)	11		
Back pain			
subjects affected / exposed	8 / 68 (11.76%)		
occurrences (all)	11		
Myalgia			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		
Pain in extremity			

subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	4		
Infections and infestations			
COVID-19			
subjects affected / exposed	6 / 68 (8.82%)		
occurrences (all)	6		
Oral herpes			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	6		
Upper respiratory tract infection			
subjects affected / exposed	9 / 68 (13.24%)		
occurrences (all)	10		
Tonsillitis			
subjects affected / exposed	4 / 68 (5.88%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	5 / 68 (7.35%)		
occurrences (all)	7		
Hyperuricaemia			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 August 2018	• For CT, PET, and disease-related constitutional symptom assessments, the first assessment was moved from Week 8 to Week 12. • Updated inclusion criteria to 1) ensure that subjects with WM were not included in this study; 2) ensure that all subjects had either available archival tumor tissue or underwent a tumor biopsy; and 3) update definition of measurable disease to align with the Lugano classification criteria. • Updated to collect 12-lead ECG data only at screening and as clinically indicated. • Updated to provide guidance on the risk of opportunistic infections, including Pneumocystis jiroveci pneumonia.
20 September 2019	• Updated to correct errors and clarify content where needed. • Increased the number of study centers to approximately 60. • Updated inclusion criteria to 1) list specific MZL symptoms dictating the need for systemic therapy; 2) remove an incorrect statement; and 3) update contraception information for female subjects of childbearing potential for consistency across BeiGene protocols and clarity. • Added to exclusion criteria: In France only, subjects whose ejection fraction is < 45% should not enter the study.
03 June 2020	• Extended the time window of the primary efficacy analysis to 12 months (after the last subject received the first dose of study drug).

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/34526366