Clinical trial results:
A Phase 2, Open-Label, 2-Cohort, Multicenter Study of INCB050465, a PI3K Inhibitor, in Relapsed or Refractory Mantle Cell Lymphoma Previously Treated With or Without a BTK Inhibitor

Summary

EudraCT number	2017-003148-19
Trial protocol	DK GB CZ BE ES IT
Global end of trial date	30 April 2024

Results information

Result version number	v1
This version publication date	16 February 2025
First version publication date	16 February 2025

Trial information

Trial identification

Sponsor protocol code	INCB 50465-205 (CITADEL-205)

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Incyte Corporation
Sponsor organisation address	1801 Augustine Cutoff Drive, Wilmington, United States, 19803
Public contact	Study Director, Incyte Corporation, 1 8554633463, medinfo@incyte.com
Scientific contact	Study Director, Incyte Corporation, 1 8554633463, medinfo@incyte.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	30 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was conducted to assess the efficacy of INCB050465 in terms of objective response rate (ORR) in participants with mantle cell lymphoma (MCL) that was relapsed or refractory after at least 1 but no more than 3 prior systemic treatment regimens.

Protection of trial subjects:

This study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, GoodClinical Practices as defined in Title 21 of the United States Code of Federal Regulations Parts 11, 50, 54, 56, and 312, as well as International Council on Harmonisation GoodClinical Practice consolidated guidelines (E6) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 November 2017
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: 5
Country: Number of subjects enrolled	Czechia: 12
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	France: 28
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	161
EEA total number of subjects	124

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)	39
From 65 to 84 years	115
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 76 investigative sites in France, Spain, the United States, Italy, Poland, Czech Republic, Great Britain, Denmark, Belgium, Germany, and Israel.

Pre-assignment

Screening details:

A total of 161 participants with relapsed or refractory mantle cell lymphoma who received 1-3 prior systemic therapies were enrolled. An additional participant was enrolled but not treated; he/she was not assigned to any treatment/cohort and was not included in the "Full Analysis Set" or "Safety Population" for analysis.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Treatment A (Exposed to Ibrutinib)

Arm description:

Participants received parsaclisib 20 milligrams (mg), orally, once daily (QD) for 8 weeks followed by 20 mg once weekly (QW) for up to 52 weeks. Participants who were exposed to ibrutinib before enrollment were included in this group.

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

Dosage and administration details:

1 mg, 2.5 mg, 5 mg, and 20 mg tablets taken orally

Arm title	Cohort 1: Treatment B (Exposed to Ibrutinib)

Arm description:

Participants received parsaclisib 20 mg, orally, QD for 8 weeks followed by 2.5 mg QD for up to 116 weeks. Participants who were exposed to ibrutinib before enrollment were included in this group.

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

Dosage and administration details:

1 mg, 2.5 mg, 5 mg, and 20 mg tablets taken orally

Arm title	Cohort 2: Treatment A (BTK Inhibitor Naïve)

Arm description:

Participants received parsaclisib 20 mg, orally, QD for 8 weeks followed by 20 mg QW for up to approximately 145 weeks. Participants who were not exposed to BTK inhibitor before enrollment were included in this group.

Arm type	Experimental

Investigational medicinal product name	parsaclisib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 mg, 2.5 mg, 5 mg, and 20 mg tablets taken orally

Arm title	Cohort 2: Treatment B (BTK Inhibitor Naïve)

Arm description:

Participants received parsaclisib 20 mg, orally, QD for 8 weeks followed by 2.5 mg QD for up to approximately 136 weeks. Participants who were not exposed to BTK inhibitor before enrollment were included in this group.

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

Dosage and administration details:

1 mg, 2.5 mg, 5 mg, and 20 mg tablets taken orally

Number of subjects in period 1	Cohort 1: Treatment A (Exposed to Ibrutinib)	Cohort 1: Treatment B (Exposed to Ibrutinib)	Cohort 2: Treatment A (BTK Inhibitor Naïve)
Started	12	41	31
Completed	1	5	8
Not completed	11	36	23
Adverse event, serious fatal	11	31	19
Consent withdrawn by subject	-	3	1
Participant Transitioned to Rollover Protocol	-	-	2
Discomfort, Pain, and Radiographic Advancement	-	-	-
Lost to follow-up	-	1	1
Disease Progression	-	1	-

Number of subjects in period 1	Cohort 2: Treatment B (BTK Inhibitor Naïve)
Started	77
Completed	29
Not completed	48
Adverse event, serious fatal	34
Consent withdrawn by subject	5
Participant Transitioned to Rollover Protocol	5
Discomfort, Pain, and Radiographic Advancement	1
Lost to follow-up	1

Disease Progression	2

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Treatment A (Exposed to Ibrutinib)
Reporting group description:	
Participants received parsaclisib 20 milligrams (mg), orally, once daily (QD) for 8 weeks followed by 20 mg once weekly (QW) for up to 52 weeks. Participants who were exposed to ibrutinib before enrollment were included in this group.	
Reporting group title	Cohort 1: Treatment B (Exposed to Ibrutinib)
Reporting group description:	
Participants received parsaclisib 20 mg, orally, QD for 8 weeks followed by 2.5 mg QD for up to 116 weeks. Participants who were exposed to ibrutinib before enrollment were included in this group.	
Reporting group title	Cohort 2: Treatment A (BTK Inhibitor Naïve)
Reporting group description:	
Participants received parsaclisib 20 mg, orally, QD for 8 weeks followed by 20 mg QW for up to approximately 145 weeks. Participants who were not exposed to BTK inhibitor before enrollment were included in this group.	
Reporting group title	Cohort 2: Treatment B (BTK Inhibitor Naïve)
Reporting group description:	
Participants received parsaclisib 20 mg, orally, QD for 8 weeks followed by 2.5 mg QD for up to approximately 136 weeks. Participants who were not exposed to BTK inhibitor before enrollment were included in this group.	

Reporting group values	Cohort 1: Treatment A (Exposed to Ibrutinib)	Cohort 1: Treatment B (Exposed to Ibrutinib)	Cohort 2: Treatment A (BTK Inhibitor Naïve)
Number of subjects	12	41	31
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	12	6
From 65-84 years	8	28	22
85 years and over	0	1	3
Age Continuous Units: years			
arithmetic mean	70.2	69.8	72.2
full range (min-max)	53 to 82	48 to 89	43 to 89
Sex: Female, Male Units: participants			
Female	1	11	5
Male	11	30	26
Ethnicity, Customized Units: Subjects			
Hispanic or Latino	3	2	4
Not Hispanic or Latino	6	28	21
Not Reported	1	5	6

Unknown	2	4	0
Captured as "Other" in Database	0	0	0
Missing	0	2	0
Race, Customized Units: Subjects			
White	11	37	24
Black or African American	0	0	0
Asian	0	0	0
American-Indian/Alaska Native	0	0	0
Native Hawaiian/Pacific Islander	0	0	0
Captured as "Other" in Database	1	1	5
Missing	0	3	2

Reporting group values	Cohort 2: Treatment B (BTK Inhibitor Naïve)	Total	
Number of subjects	77	161	
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)	17	39	
From 65-84 years	57	115	
85 years and over	3	7	
Age Continuous Units: years			
arithmetic mean	71.5		
full range (min-max)	51 to 90	-	
Sex: Female, Male Units: participants			
Female	17	34	
Male	60	127	
Ethnicity, Customized Units: Subjects			
Hispanic or Latino	5	14	
Not Hispanic or Latino	57	112	
Not Reported	8	20	
Unknown	1	7	
Captured as "Other" in Database	2	2	
Missing	4	6	
Race, Customized Units: Subjects			
White	64	136	
Black or African American	2	2	
Asian	1	1	
American-Indian/Alaska Native	0	0	
Native Hawaiian/Pacific Islander	0	0	

Captured as "Other" in Database	3	10	
Missing	7	12	

End points

End points reporting groups

Reporting group title	Cohort 1: Treatment A (Exposed to Ibrutinib)
Reporting group description:	
Participants received parsaclisib 20 milligrams (mg), orally, once daily (QD) for 8 weeks followed by 20 mg once weekly (QW) for up to 52 weeks. Participants who were exposed to ibrutinib before enrollment were included in this group.	
Reporting group title	Cohort 1: Treatment B (Exposed to Ibrutinib)
Reporting group description:	
Participants received parsaclisib 20 mg, orally, QD for 8 weeks followed by 2.5 mg QD for up to 116 weeks. Participants who were exposed to ibrutinib before enrollment were included in this group.	
Reporting group title	Cohort 2: Treatment A (BTK Inhibitor Naïve)
Reporting group description:	
Participants received parsaclisib 20 mg, orally, QD for 8 weeks followed by 20 mg QW for up to approximately 145 weeks. Participants who were not exposed to BTK inhibitor before enrollment were included in this group.	
Reporting group title	Cohort 2: Treatment B (BTK Inhibitor Naïve)
Reporting group description:	
Participants received parsaclisib 20 mg, orally, QD for 8 weeks followed by 2.5 mg QD for up to approximately 136 weeks. Participants who were not exposed to BTK inhibitor before enrollment were included in this group.	

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]
End point description:	
ORR=percentage of participants with complete response(CR) or partial response(PR) per revised response criteria for lymphomas,determined by independent review committee(IRC).Criteria for CR:1.Target nodes/nodal masses of lymph nodes,extralymphatic sites regressed to≤1.5cm in longest dimension transverse diameter of lesion(LDi);2.Absence of non-measured lesion;3.Organ enlargement regressed to normal;4.No new lesions;5.Normal bone marrow morphology;if indeterminate,immunohistochemistry negative.Criteria for PR:1.Lymph nodes,extralymphatic sites-≥50%decrease in sum of product of perpendicular diameters for multiple lesions(SPD)of up to 6 target measurable nodes,extranodal sites;if lesion is too small to measure on computed tomography(CT),assign5mm×5mm as default;if no longer visible,0×0mm.Node>5mm×5mm but smaller than normal,use actual measurement.2.Absent/regressed non-measured lesions,no increase.3.Organ enlargement-Spleen regressed by>50%in length beyond normal.4.No new lesions.	
End point type	Primary
End point timeframe:	
Up to 1016 days	

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: Statistical analysis was not conducted for this endpoint.

End point values	Cohort 1: Treatment A (Exposed to Ibrutinib)	Cohort 1: Treatment B (Exposed to Ibrutinib)	Cohort 2: Treatment A (BTK Inhibitor Naïve)	Cohort 2: Treatment B (BTK Inhibitor Naïve)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[2]	41[3]	31[4]	77[5]
Units: percentage of participants				
number (confidence interval 95%)	8.3 (0.2 to 38.5)	39.0 (24.2 to 55.5)	64.5 (45.4 to 80.8)	71.4 (60.0 to 81.2)

Notes:

[2] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

[3] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

[4] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

[5] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate (CRR)

End point title	Complete Response Rate (CRR)

End point description:

CRR is defined as the percentage of participants with a CR as defined by response criteria for lymphomas, as determined by an IRC. The criteria for CR included: 1.Target nodes/nodal masses of lymph nodes and extralymphatic sites must regress to ≤ 1.5 cm in LDi; 2. Absence of non-measured lesion; 3.Organ enlargement regressed to normal; 4.No new lesions; 5.Bone marrow must be normal by morphology; if indeterminate, immunohistochemistry negative.

End point type	Secondary

End point timeframe:

Up to 1016 days

End point values	Cohort 1: Treatment A (Exposed to Ibrutinib)	Cohort 1: Treatment B (Exposed to Ibrutinib)	Cohort 2: Treatment A (BTK Inhibitor Naïve)	Cohort 2: Treatment B (BTK Inhibitor Naïve)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[6]	41[7]	31[8]	77[9]
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 26.5)	2.4 (0.1 to 12.9)	22.6 (9.6 to 41.1)	15.6 (8.3 to 25.6)

Notes:

[6] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

[7] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

[8] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

[9] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR=time from first documented evidence of CR/PR until disease progression/death from any cause as determined by IRC. CR: 1.Target nodes/nodal masses of lymph nodes/extralymphatic sites regressed to ≤1.5 cm in LDi; 2. Absence of non-measured lesion; 3.Organ enlargement regressed to normal; 4.No new lesions; 5.Bone marrow normal by morphology; if indeterminate, immunohistochemistry negative. PR: 1.Lymph nodes/extralymphatic sites- a. ≥50% decrease in SPD of up to 6 target measurable nodes/extranodal sites; b. when a lesion is too small to measure on CT, assign 5 mm×5 mm as the default; c.when no longer visible, 0×0 mm. For a node >5 mm×5 mm but smaller than normal, use actual measurement. 2.Non-measured lesions- Absent/regressed, but no increase. 3. Organ enlargement-Spleen regressed by >50% in length beyond normal. 4.No new lesions. -999, 9999=The

upper limit of the CI was not estimable due to the low number of participants with events.

End point type	Secondary

End point timeframe:

Up to 1016 days

End point values	Cohort 1: Treatment A (Exposed to Ibrutinib)	Cohort 1: Treatment B (Exposed to Ibrutinib)	Cohort 2: Treatment A (BTK Inhibitor Naïve)	Cohort 2: Treatment B (BTK Inhibitor Naïve)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1[10]	16[11]	20[12]	55[13]
Units: months				
median (confidence interval 95%)	9999 (-9999 to 9999)	3.20 (1.87 to 7.95)	17.45 (3.81 to 9999)	13.01 (9.03 to 16.59)

Notes:

[10] - Only participants with objective response were analyzed.

[11] - Only participants with objective response were analyzed.

[12] - Only participants with objective response were analyzed.

[13] - Only participants with objective response were analyzed.

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 the date of the first dose of study treatment until death from any cause. 9999=The upper limit of the confidence interval was not estimable because too few participants died.

End point type	Secondary

End point timeframe:

Up to 1016 days

End point values	Cohort 1: Treatment A (Exposed to Ibrutinib)	Cohort 1: Treatment B (Exposed to Ibrutinib)	Cohort 2: Treatment A (BTK Inhibitor Naïve)	Cohort 2: Treatment B (BTK Inhibitor Naïve)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[14]	41[15]	31[16]	77[17]
Units: months				
median (confidence interval 95%)	10.91 (1.35 to 17.64)	11.01 (7.23 to 17.12)	33.48 (21.62 to 54.67)	45.86 (34.20 to 9999)

Notes:

[14] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

[15] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

[16] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

[17] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS is defined as the time from the date of the first dose of study treatment until the earliest date of disease progression as determined by radiographic disease assessment provided by an IRC, or death from any cause. 9999=The upper limit of the 95% CI was not estimable due to the low number of participants with events.

End point type	Secondary

End point timeframe:

Up to 1016 days

End point values	Cohort 1: Treatment A (Exposed to Ibrutinib)	Cohort 1: Treatment B (Exposed to Ibrutinib)	Cohort 2: Treatment A (BTK Inhibitor Naïve)	Cohort 2: Treatment B (BTK Inhibitor Naïve)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[18]	41[19]	31[20]	77[21]
Units: months				
median (confidence interval 95%)	3.94 (1.35 to 9999)	3.68 (1.87 to 5.49)	8.11 (5.29 to 21.62)	13.83 (10.02 to 16.89)

Notes:

[18] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

[19] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

[20] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

[21] - Full Analysis Set: all participants enrolled in the study who received ≥1 dose of parsaclisib

Statistical analyses

No statistical analyses for this end point

Secondary: Best Percent Change from Baseline in Target Lesion Size

End point title	Best Percent Change from Baseline in Target Lesion Size

End point description:

Target lesion size is measured by the sum of the product of diameters of all target lesion sizes and is determined by the IRC. The best percent change from Baseline is defined as the largest decrease, or smallest increase if no decrease available, from Baseline in target lesion sizes on/before new (next-line) anti-lymphoma therapy during the study. Baseline is the last nonmissing measurement obtained before the first administration of study drug. A negative percent change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Up to 1016 days

End point values	Cohort 1: Treatment A (Exposed to Ibrutinib)	Cohort 1: Treatment B (Exposed to Ibrutinib)	Cohort 2: Treatment A (BTK Inhibitor Naïve)	Cohort 2: Treatment B (BTK Inhibitor Naïve)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6[22]	32[23]	25[24]	68[25]
Units: percent change in lesion size				
arithmetic mean (standard deviation)	-19.82 (± 35.926)	-9.51 (± 133.438)	-64.65 (± 53.360)	-67.54 (± 32.918)

Notes:

[22] - Full Analysis Set. Only participants with available data were analyzed.

[23] - Full Analysis Set. Only participants with available data were analyzed.

[24] - Full Analysis Set. Only participants with available data were analyzed.

[25] - Full Analysis Set. Only participants with available data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point description:

An adverse event (AE) is any untoward medical occurrence associated with use of a drug in humans, whether or not considered drug related, that occurs after a participant provides informed consent. A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug and within 30 days of the last administration of study drug regardless of starting new anti-lymphoma therapy. A SAE is any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, leads to a congenital anomaly/birth defect or is considered to be an important medical event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant or require medical or surgical intervention.

End point type	Secondary

End point timeframe:

From first dose of study drug up to 2045 days

End point values	Cohort 1: Treatment A (Exposed to Ibrutinib)	Cohort 1: Treatment B (Exposed to Ibrutinib)	Cohort 2: Treatment A (BTK Inhibitor Naïve)	Cohort 2: Treatment B (BTK Inhibitor Naïve)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[26]	41[27]	31[28]	77[29]
Units: percentage of participants				
number (not applicable)				
TEAEs	83.3	90.2	93.5	92.2
SAEs	41.7	48.8	38.7	58.4

Notes:

[26] - Safety Population: all enrolled participants who received ≥1 dose of parsaclisib

[27] - Safety Population: all enrolled participants who received ≥1 dose of parsaclisib

[28] - Safety Population: all enrolled participants who received ≥1 dose of parsaclisib

[29] - Safety Population: all enrolled participants who received ≥1 dose of parsaclisib

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 2045 days

Adverse event reporting additional description:

Adverse events have been reported for members of the Safety Population, comprised of all enrolled participants who received at least 1 dose of parsaclisib.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Cohort 1: Treatment B (Exposed to Ibrutinib)

Reporting group description:

Participants received parsaclisib 20 mg, orally, QD for 8 weeks followed by 2.5 mg QD for up to 116 weeks. Participants who were exposed to ibrutinib before enrollment were included in this group.

Reporting group title	Cohort 1: Treatment A (Exposed to Ibrutinib)

Reporting group description:

Participants received parsaclisib 20 milligrams (mg), orally, once daily (QD) for 8 weeks followed by 20 mg once weekly (QW) for up to 52 weeks. Participants who were exposed to ibrutinib before enrollment were included in this group.

Reporting group title	Cohort 2: Treatment B (BTK Inhibitor Naïve)

Reporting group description:

Participants received parsaclisib 20 mg, orally, QD for 8 weeks followed by 2.5 mg QD for up to approximately 136 weeks. Participants who were not exposed to BTK inhibitor before enrollment were included in this group.

Reporting group title	Total

Reporting group description:

Total

Reporting group title	Cohort 2: Treatment A (BTK Inhibitor Naïve)

Reporting group description:

Participants received parsaclisib 20 mg, orally, QD for 8 weeks followed by 20 mg QW for up to approximately 145 weeks. Participants who were not exposed to BTK inhibitor before enrollment were included in this group.

Serious adverse events	Cohort 1: Treatment B (Exposed to Ibrutinib)	Cohort 1: Treatment A (Exposed to Ibrutinib)	Cohort 2: Treatment B (BTK Inhibitor Naïve)
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 41 (48.78%)	5 / 12 (41.67%)	45 / 77 (58.44%)
number of deaths (all causes)	31	11	34
number of deaths resulting from adverse events	3	1	8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myelomonocytic leukaemia			

subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mantle cell lymphoma			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hyperthermia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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

Oedema peripheral			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Nodule			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Peripheral swelling			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Swelling			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
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			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Neutrophil count decreased			

subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Spinal fracture			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia supraventricular			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ischaemic stroke			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	0 / 77 (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	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Leukocytosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Neutropenia			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	0 / 77 (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
Autoimmune colitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ascites			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	6 / 77 (7.79%)
occurrences causally related to treatment / all	2 / 2	0 / 0	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 41 (7.32%)	1 / 12 (8.33%)	11 / 77 (14.29%)
occurrences causally related to treatment / all	2 / 6	1 / 1	10 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Intestinal perforation			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis ulcerative			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Nausea			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis psoriasiform			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis exfoliative			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Eczema			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal failure			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oligoarthritis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Spondylitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

COVID-19			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cytomegalovirus infection reactivation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Cytomegalovirus colitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Clostridium difficile colitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Endocarditis staphylococcal			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Parainfluenzae virus infection			

subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Septic shock			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
Urosepsis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (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
Dehydration			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Total	Cohort 2: Treatment A (BTK Inhibitor Naïve)	
Total subjects affected by serious adverse events			
subjects affected / exposed	82 / 161 (50.93%)	12 / 31 (38.71%)	
number of deaths (all causes)	95	19	
number of deaths resulting from adverse events	12	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myelomonocytic leukaemia			

subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 161 (0.62%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mantle cell lymphoma			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 161 (0.62%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oedema peripheral			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodule			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 161 (2.48%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Swelling			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 161 (0.62%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 161 (1.24%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutrophil count decreased			

subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 161 (0.62%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia supraventricular			
subjects affected / exposed	1 / 161 (0.62%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 161 (1.24%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 161 (0.62%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ischaemic stroke			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 161 (1.24%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ascites			
subjects affected / exposed	1 / 161 (0.62%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	8 / 161 (4.97%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	8 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	15 / 161 (9.32%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	13 / 18	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis ulcerative			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	1 / 161 (0.62%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis psoriasiform			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 161 (2.48%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal failure			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oligoarthritis			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylitis			
subjects affected / exposed	1 / 161 (0.62%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

COVID-19			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cytomegalovirus infection reactivation			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis staphylococcal			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infection			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Parainfluenzae virus infection			

subjects affected / exposed	1 / 161 (0.62%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 161 (1.86%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 161 (0.62%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypokalaemia			
subjects affected / exposed	4 / 161 (2.48%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	1 / 161 (0.62%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1: Treatment B (Exposed to Ibrutinib)	Cohort 1: Treatment A (Exposed to Ibrutinib)	Cohort 2: Treatment B (BTK Inhibitor Naïve)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 41 (68.29%)	9 / 12 (75.00%)	66 / 77 (85.71%)
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 41 (2.44%)	1 / 12 (8.33%)	4 / 77 (5.19%)
occurrences (all)	1	1	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 41 (17.07%)	0 / 12 (0.00%)	11 / 77 (14.29%)
occurrences (all)	7	0	14
Fatigue			
subjects affected / exposed	2 / 41 (4.88%)	2 / 12 (16.67%)	8 / 77 (10.39%)
occurrences (all)	2	2	8
Oedema peripheral			
subjects affected / exposed	3 / 41 (7.32%)	2 / 12 (16.67%)	5 / 77 (6.49%)
occurrences (all)	4	3	5
Pyrexia			
subjects affected / exposed	6 / 41 (14.63%)	1 / 12 (8.33%)	12 / 77 (15.58%)
occurrences (all)	6	1	15
Reproductive system and breast disorders			
Testicular oedema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 41 (7.32%)	1 / 12 (8.33%)	4 / 77 (5.19%)
occurrences (all)	3	1	4
Cough			
subjects affected / exposed	5 / 41 (12.20%)	1 / 12 (8.33%)	12 / 77 (15.58%)
occurrences (all)	5	1	13
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 41 (4.88%)	1 / 12 (8.33%)	0 / 77 (0.00%)
occurrences (all)	2	1	0
Insomnia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 12 (16.67%)	3 / 77 (3.90%)
occurrences (all)	0	2	3
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	4 / 77 (5.19%)
occurrences (all)	1	0	4
Blood creatinine increased			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	5 / 77 (6.49%)
occurrences (all)	3	0	7
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	5 / 77 (6.49%)
occurrences (all)	1	0	6
Neutrophil count decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	9
Platelet count decreased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	2 / 77 (2.60%)
occurrences (all)	0	1	2
Respiratory rate increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Pseudomonas test positive			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	3 / 41 (7.32%)	2 / 12 (16.67%)	10 / 77 (12.99%)
occurrences (all)	3	2	12
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	2 / 41 (4.88%)	1 / 12 (8.33%)	1 / 77 (1.30%)
occurrences (all)	2	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 41 (4.88%)	2 / 12 (16.67%)	1 / 77 (1.30%)
occurrences (all)	2	2	1
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	8 / 41 (19.51%)	3 / 12 (25.00%)	6 / 77 (7.79%)
occurrences (all)	10	4	9
Eosinophilia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	3 / 77 (3.90%)
occurrences (all)	0	0	3
Neutropenia			
subjects affected / exposed	6 / 41 (14.63%)	2 / 12 (16.67%)	10 / 77 (12.99%)
occurrences (all)	9	2	12
Thrombocytopenia			
subjects affected / exposed	3 / 41 (7.32%)	1 / 12 (8.33%)	5 / 77 (6.49%)
occurrences (all)	5	1	6
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 41 (2.44%)	1 / 12 (8.33%)	1 / 77 (1.30%)
occurrences (all)	1	1	1
Abdominal pain			
subjects affected / exposed	3 / 41 (7.32%)	0 / 12 (0.00%)	4 / 77 (5.19%)
occurrences (all)	3	0	4
Eructation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Dysphagia			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	1 / 77 (1.30%)
occurrences (all)	2	0	1
Dyspepsia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	3 / 77 (3.90%)
occurrences (all)	0	0	3
Diarrhoea			

subjects affected / exposed	9 / 41 (21.95%)	2 / 12 (16.67%)	26 / 77 (33.77%)
occurrences (all)	18	3	40
Constipation			
subjects affected / exposed	4 / 41 (9.76%)	0 / 12 (0.00%)	12 / 77 (15.58%)
occurrences (all)	5	0	13
Colitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	3 / 77 (3.90%)
occurrences (all)	0	1	3
Nausea			
subjects affected / exposed	2 / 41 (4.88%)	2 / 12 (16.67%)	8 / 77 (10.39%)
occurrences (all)	3	2	8
Stomatitis			
subjects affected / exposed	1 / 41 (2.44%)	1 / 12 (8.33%)	2 / 77 (2.60%)
occurrences (all)	1	1	2
Vomiting			
subjects affected / exposed	2 / 41 (4.88%)	1 / 12 (8.33%)	4 / 77 (5.19%)
occurrences (all)	2	1	4
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	5 / 77 (6.49%)
occurrences (all)	1	0	5
Hyperhidrosis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 41 (2.44%)	1 / 12 (8.33%)	6 / 77 (7.79%)
occurrences (all)	2	1	6
Rash			
subjects affected / exposed	4 / 41 (9.76%)	1 / 12 (8.33%)	16 / 77 (20.78%)
occurrences (all)	4	1	19
Rash maculo-papular			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	3 / 77 (3.90%)
occurrences (all)	2	0	3
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	1 / 41 (2.44%)	2 / 12 (16.67%)	3 / 77 (3.90%)
occurrences (all)	2	2	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 41 (9.76%)	0 / 12 (0.00%)	5 / 77 (6.49%)
occurrences (all)	4	0	6
Back pain			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	6 / 77 (7.79%)
occurrences (all)	2	0	6
Pain in extremity			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	2 / 77 (2.60%)
occurrences (all)	2	0	3
Myalgia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	4 / 77 (5.19%)
occurrences (all)	0	0	4
Muscle spasms			
subjects affected / exposed	2 / 41 (4.88%)	0 / 12 (0.00%)	2 / 77 (2.60%)
occurrences (all)	2	0	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	2 / 77 (2.60%)
occurrences (all)	1	0	2
COVID-19			
subjects affected / exposed	0 / 41 (0.00%)	0 / 12 (0.00%)	4 / 77 (5.19%)
occurrences (all)	0	0	4
Nasopharyngitis			
subjects affected / exposed	1 / 41 (2.44%)	2 / 12 (16.67%)	3 / 77 (3.90%)
occurrences (all)	2	3	4
Rhinitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 41 (2.44%)	1 / 12 (8.33%)	2 / 77 (2.60%)
occurrences (all)	2	1	3
Upper respiratory tract infection			

subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	3 / 77 (3.90%)
occurrences (all)	1	0	3
Viral infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 41 (9.76%)	2 / 12 (16.67%)	7 / 77 (9.09%)
occurrences (all)	4	2	7
Hypernatraemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 12 (8.33%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Hyperuricaemia			
subjects affected / exposed	2 / 41 (4.88%)	1 / 12 (8.33%)	3 / 77 (3.90%)
occurrences (all)	4	1	6
Malnutrition			
subjects affected / exposed	0 / 41 (0.00%)	1 / 12 (8.33%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	2 / 77 (2.60%)
occurrences (all)	1	0	2
Hypokalaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 12 (0.00%)	12 / 77 (15.58%)
occurrences (all)	1	0	16

Non-serious adverse events	Total	Cohort 2: Treatment A (BTK Inhibitor Naïve)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	130 / 161 (80.75%)	27 / 31 (87.10%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 161 (4.35%)	1 / 31 (3.23%)	
occurrences (all)	7	1	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	21 / 161 (13.04%)	3 / 31 (9.68%)	
occurrences (all)	24	3	
Fatigue			
subjects affected / exposed	14 / 161 (8.70%)	2 / 31 (6.45%)	
occurrences (all)	14	2	
Oedema peripheral			
subjects affected / exposed	12 / 161 (7.45%)	2 / 31 (6.45%)	
occurrences (all)	14	2	
Pyrexia			
subjects affected / exposed	24 / 161 (14.91%)	5 / 31 (16.13%)	
occurrences (all)	27	5	
Reproductive system and breast disorders			
Testicular oedema			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	11 / 161 (6.83%)	3 / 31 (9.68%)	
occurrences (all)	11	3	
Cough			
subjects affected / exposed	20 / 161 (12.42%)	2 / 31 (6.45%)	
occurrences (all)	21	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 161 (1.86%)	0 / 31 (0.00%)	
occurrences (all)	3	0	
Insomnia			
subjects affected / exposed	5 / 161 (3.11%)	0 / 31 (0.00%)	
occurrences (all)	5	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 161 (3.73%)	1 / 31 (3.23%)	
occurrences (all)	6	1	
Blood creatinine increased			

subjects affected / exposed	9 / 161 (5.59%)	2 / 31 (6.45%)	
occurrences (all)	13	3	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 161 (3.73%)	0 / 31 (0.00%)	
occurrences (all)	7	0	
Neutrophil count decreased			
subjects affected / exposed	4 / 161 (2.48%)	2 / 31 (6.45%)	
occurrences (all)	11	2	
Platelet count decreased			
subjects affected / exposed	5 / 161 (3.11%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
Respiratory rate increased			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Pseudomonas test positive			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	15 / 161 (9.32%)	0 / 31 (0.00%)	
occurrences (all)	17	0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	4 / 161 (2.48%)	0 / 31 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 161 (4.97%)	3 / 31 (9.68%)	
occurrences (all)	9	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 161 (13.04%)	4 / 31 (12.90%)	
occurrences (all)	27	4	
Eosinophilia			

subjects affected / exposed	5 / 161 (3.11%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
Neutropenia			
subjects affected / exposed	21 / 161 (13.04%)	3 / 31 (9.68%)	
occurrences (all)	27	4	
Thrombocytopenia			
subjects affected / exposed	11 / 161 (6.83%)	2 / 31 (6.45%)	
occurrences (all)	14	2	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 161 (1.86%)	0 / 31 (0.00%)	
occurrences (all)	3	0	
Abdominal pain			
subjects affected / exposed	8 / 161 (4.97%)	1 / 31 (3.23%)	
occurrences (all)	8	1	
Eructation			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	5 / 161 (3.11%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
Dyspepsia			
subjects affected / exposed	5 / 161 (3.11%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
Diarrhoea			
subjects affected / exposed	45 / 161 (27.95%)	8 / 31 (25.81%)	
occurrences (all)	72	11	
Constipation			

subjects affected / exposed	19 / 161 (11.80%)	3 / 31 (9.68%)	
occurrences (all)	21	3	
Colitis			
subjects affected / exposed	4 / 161 (2.48%)	0 / 31 (0.00%)	
occurrences (all)	4	0	
Nausea			
subjects affected / exposed	16 / 161 (9.94%)	4 / 31 (12.90%)	
occurrences (all)	17	4	
Stomatitis			
subjects affected / exposed	5 / 161 (3.11%)	1 / 31 (3.23%)	
occurrences (all)	5	1	
Vomiting			
subjects affected / exposed	9 / 161 (5.59%)	2 / 31 (6.45%)	
occurrences (all)	9	2	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	6 / 161 (3.73%)	0 / 31 (0.00%)	
occurrences (all)	6	0	
Hyperhidrosis			
subjects affected / exposed	2 / 161 (1.24%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Pruritus			
subjects affected / exposed	9 / 161 (5.59%)	1 / 31 (3.23%)	
occurrences (all)	10	1	
Rash			
subjects affected / exposed	23 / 161 (14.29%)	2 / 31 (6.45%)	
occurrences (all)	26	2	
Rash maculo-papular			
subjects affected / exposed	7 / 161 (4.35%)	2 / 31 (6.45%)	
occurrences (all)	7	2	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	6 / 161 (3.73%)	0 / 31 (0.00%)	
occurrences (all)	9	0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	11 / 161 (6.83%)	2 / 31 (6.45%)	
occurrences (all)	12	2	
Back pain			
subjects affected / exposed	12 / 161 (7.45%)	4 / 31 (12.90%)	
occurrences (all)	12	4	
Pain in extremity			
subjects affected / exposed	6 / 161 (3.73%)	2 / 31 (6.45%)	
occurrences (all)	7	2	
Myalgia			
subjects affected / exposed	5 / 161 (3.11%)	1 / 31 (3.23%)	
occurrences (all)	6	2	
Muscle spasms			
subjects affected / exposed	6 / 161 (3.73%)	2 / 31 (6.45%)	
occurrences (all)	6	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 161 (3.11%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
COVID-19			
subjects affected / exposed	6 / 161 (3.73%)	2 / 31 (6.45%)	
occurrences (all)	6	2	
Nasopharyngitis			
subjects affected / exposed	8 / 161 (4.97%)	2 / 31 (6.45%)	
occurrences (all)	11	2	
Rhinitis			
subjects affected / exposed	3 / 161 (1.86%)	2 / 31 (6.45%)	
occurrences (all)	3	2	
Urinary tract infection			
subjects affected / exposed	7 / 161 (4.35%)	3 / 31 (9.68%)	
occurrences (all)	10	4	
Upper respiratory tract infection			
subjects affected / exposed	6 / 161 (3.73%)	2 / 31 (6.45%)	
occurrences (all)	6	2	
Viral infection			

subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 161 (8.70%)	1 / 31 (3.23%)	
occurrences (all)	14	1	
Hypernatraemia			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia			
subjects affected / exposed	2 / 161 (1.24%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Hyperuricaemia			
subjects affected / exposed	8 / 161 (4.97%)	2 / 31 (6.45%)	
occurrences (all)	13	2	
Malnutrition			
subjects affected / exposed	1 / 161 (0.62%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Hypophosphataemia			
subjects affected / exposed	5 / 161 (3.11%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
Hypokalaemia			
subjects affected / exposed	13 / 161 (8.07%)	0 / 31 (0.00%)	
occurrences (all)	17	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 November 2017	The primary purpose of this amendment was to address changes requested by the European Regulatory Agency.
31 January 2018	The primary purpose of this amendment was to institute hematology testing every 2 weeks for the first 8 weeks of dosing.
16 July 2018	The primary purpose of this amendment was to modify the dose reduction schedules.
07 December 2018	The primary purpose of the amendment was to increase the number of participants in each cohort to better understand the safety and efficacy of INCB050465 administered at one of the two treatment regimens.
29 August 2019	The primary purpose of this amendment was to add 10 more participants to Cohort 2.
23 December 2019	The primary purpose of this amendment was to provide additional guidance on dose modification in the event of diarrhea and colitis and to define the end of the study, including the option to receive continued treatment with INCB050465 in a rollover protocol.
30 January 2020	The primary purpose of this amendment was to close enrollment for Cohort 1 before reaching the target enrollment (n = 90).
07 September 2022	The primary purpose of this amendment was to describe risks associated with COVID-19.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported