Sponsor

Novartis

Generic Drug Name

Ruxolitinib (INC424) and buparlisib (BKM120)

Trial Indication(s)

Myelofibrosis

Protocol Number

CINC424A2104

Protocol Title

A phase Ib, open-label, multi-center, two-arm, dose-finding study to assess the safety and efficacy of the oral combination of Ruxolitinib (INC424) and BKM120 in patients with primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF), or post-essential thrombocythemia-myelofibrosis (PET-MF)

Clinical Trial Phase

Phase Ib

Phase of Drug Development

Phase I in combination development

Study Start/End Dates

18-Dec-2012 to 28-Sep-2017

Reason for Termination (If applicable)

The benefit/risk assessment of the combined treatment was not supportive for myelofibrosis (MF) patients (although there was some evidence of improved spleen response in ruxolitinib + buparlisib combination treatments versus ruxolitinib monotherapy, there was unfavorable increased toxicity), which contributed to the decision to terminate the study early. Additionally, considering study results in different indications, particularly in the large Phase III studies in breast cancer and the manageable but challenging safety profile of buparlisib, Novartis made the decision not to pursue further development of buparlisib. This report presents the results from the final analysis of the study (last patient last visit 28-Sep-2017).

Study Design/Methodology

This was a Phase Ib, open-label, multi-center, two-arm, dose-finding study. Two treatment arms, A and B, both received ruxolitinib and buparlisib and were enrolled simultaneously. Treatment Arm A consisted of subjects without prior JAK inhibitor

treatment. Treatment Arm B consisted of subjects with prior JAK inhibitor treatment (including ruxolitinib) who are not currently benefitting from prior JAK treatment.

Centers

15 centers in 9 countries participated in the study: Australia (2 centers), Austria (1 center), Germany (2 centers), Spain (1 center), France (1 center), United Kingdom (3 centers), Israel (2 centers), Italy (2 centers), Singapore (1 center)

Objectives:

Primary objective(s)

To establish the MTD and/or RPIID of the combination of INC424 and BKM120 when administered orally to patients with myelofibrosis who have either received or not previous JAK inhibitor treatment. The MTD and/or RPIID was evaluated independently for each treatment arm.

Secondary objective(s)

Key Secondary: To evaluate the safety of the oral co-administration of ruxolitinib and buparlisib in patients with MF.

Other Secondary: To characterize the pharmacokinetics of ruxolitinib alone and in combination with buparlisib, as well as the pharmacokinetics of buparlisib at varying doses when given in combination in patients with MF.

Test Product (s), Dose(s), and Mode(s) of Administration

Ruxolitinib tablets for oral use at a dose strength of 5 mg to be administered twice per day. Buparlisib hard gelatin capsules available at dose strengths of 10 mg and 50 mg to be administered once a day.

Statistical Methods

An adaptive Bayesian Logistic Regression Model was used for the dose escalation. The model was fitted separately for each treatment arm (arm A and arm B) using the respective Cycle 1 DLT data (i.e. absence or presence of DLT) accumulated throughout the dose escalation to model the dose-toxicity relationship of ruxolitinib and buparlisib when given in combination.

All AEs recorded during the study were listed and summarized.

The single and multiple dose pharmacokinetic parameters of ruxolitinib and buparlisib plasma concentration-time data was computed by non-compartmental analysis. Maximum plasma concentrations (Cmax), the highest observed concentration during a dose interval, and the corresponding time (Tmax) was taken from the concentration-time data. Area under the plasma concentration time curve [AUC0-tlast] from zero (pre-dose) to tlast, (where tlast is the timepoint where the last quantifiable concentration data point is observed), and zero to 8 hours [AUC0-8] was computed by the linear trapezoidal rule. Descriptive statistics, such as mean, standard deviation, geometric mean, CV%, median and range was summarized for the pharmacokinetic parameters of ruxolitinib alone and in combination with buparlisib by dose level cohort. For Tmax, only the median and range (minimum and maximum) were reported.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Patients must be diagnosed with PMF (guided by 2008 World Health Organization [WHO] criteria for PMF), PPV-MF or PET-MF (guided by IWG-MRT for PPV-MF or PET-MF) irrespective of JAK2 mutation status
- Patients with myelofibrosis requiring therapy must be classified at least as intermediate risk level 1 (1 or more prognostic factors) with at least one criteria other than age. The prognostic factors are defined by the IWG (Cervantes et al 2009)
- Patients must have palpable spleen of at least 5 cm from the costal margin to the point of greatest splenic protrusion at Screening
- Patients must have active symptoms of MF as demonstrated by one symptom score of at least 5 (0-10 point scale) or two symptom scores of at least 3 (0 to 10 point scale) on the MF Screening Symptom Form at Screening
- Platelet counts ≥75×10^9/L not reached with the aid of transfusions at Screening or Cycle 1 Day 1

Exclusion criteria

- Previous treatment with one of the following:
    - PI3K inhibitors and AKT inhibitors
    - JAK inhibitors (including ruxolitinib) that resulted in clinically significant toxicities at the discretion of the Investigator
- Patients who have had splenic irradiation within 12 months prior to Screening
- Patients with specific mood disorders
- Any history of bleeding diathesis
- Patient has a history of cardiac dysfunction
- Patients receiving the following treatments/medications:
    - An enzyme-inducing anti-epileptic drug (EIAED) within 2 weeks prior to starting study treatment
    - Medication that has a known risk to prolong the QT interval or induce Torsades de Pointes, and the treatment cannot be discontinued or switched to a different medication prior to starting study treatment
    - Treatment with a potent systemic inhibitor or a potent systemic inducer of CYP3A4 at the time of Screening and cannot be discontinued or switched to alternative medication prior to starting study treatment
    - Any regular use of drugs that interferes with coagulation or inhibits platelet function (NOTE: low doses of aspirin ≤ 150 mg/day and low molecular weight heparin are allowed)
- Patients who currently are willing candidates for a stem cell transplantation at the time of the screening assessments

Participant Flow Table

Patient disposition by arm - Total (Full analysis set)

Disposition Reason	JAK naïve N=33 n (%)	Prior JAK N=30 n (%)	Total N=63 n (%)
Subjects treated			
End of treatment	33 (100.0%)	30 (100.0%)	63 (100.0%)
Primary reasons for end of treatment			
Adverse Event(s)	12 (36.4%)	9 (30.0%)	21 (33.3%)
Subject withdrew consent	3 (9.1%)	1 (3.3%)	4 (6.3%)
Administrative problems [1]	6 (18.2%)	4 (13.3%)	10 (15.9%)
Death	2 (6.1%)	1 (3.3%)	3 (4.8%)
Disease progression	3 (9.1%)	8 (26.7%)	11 (17.5%)
Treatment duration completed	4 (12.1%)	5 (16.7%)	9 (14.3%)
Lack of efficacy	3 (9.1%)	2 (6.7%)	5 (7.9%)
Primary reasons for study evaluation completion			
Adverse Event(s)	7 (21.2%)	5 (16.7%)	12 (19.0%)
Subject withdrew consent	2 (6.1%)	1 (3.3%)	3 (4.8%)
Administrative problems	5 (15.2%)	1 (3.3%)	6 (9.5%)
Death	3 (9.1%)	4 (13.3%)	7 (11.1%)
Disease progression	3 (9.1%)	3 (10.0%)	6 (9.5%)
Follow up phase completed as per protocol	11 (33.3%)	15 (50.0%)	26 (41.3%)
Lack of efficacy	2 (6.1%)	1 (3.3%)	3 (4.8%)

- Percentage is based on N
[1] Discontinuation reason for administrative problems was early study termination

Baseline Characteristics

Demographics by arm – Total (Full analysis set)

Demographic Variable	JAK naïve N=33 n (%)	Prior JAK N=30 n (%)	Total N=63 n (%)
Age (Years)			
Mean (SD)	62.5 (10.84)	62.7 (7.33)	62.6 (9.26)
Median	64.0	62.0	63.0
Min - Max	37 - 83	50 - 79	37 - 83
Age category (years) - n (%)			
< 65	19 (57.6)	17 (56.7)	36 (57.1)
≥ 65	14 (42.4)	13 (43.3)	27 (42.9)
Gender - n (%)			
Male	20 (60.6)	20 (66.7)	40 (63.5)
Female	13 (39.4)	10 (33.3)	23 (36.5)
Race - n (%)			
Asian	1 (3.0)	3 (10.0)	4 (6.3)
Caucasian	31 (93.9)	26 (86.7)	57 (90.5)
Other	1 (3.0)	1 (3.3)	2 (3.2)
Ethnicity - n (%)			
Hispanic/Latino	4 (12.1)	5 (16.7)	9 (14.3)
Chinese	1 (3.0)	2 (6.7)	3 (4.8)
Other	28 (84.8)	23 (76.7)	51 (81.0)
ECOG-n (%)			
0	20 (60.6)	11 (36.7)	31 (49.2)
1	11 (33.3)	16 (53.3)	27 (42.9)
2	2 (6.1)	3 (10.0)	5 (7.9)

Summary of Efficacy

Primary Outcome Result(s)

Dose-limiting toxicities occurring during the first 28 days by primary system organ class, preferred term and arm (Dose determining Set)

The MTD and RPIID was determined to be INC424 15 mg BID + BKM120 60 mg QD for both the JAK naive and Prior JAK arms.

Primary system organ class (Preferred Term)	JAK naïve N=27 n(%)	Prior JAK N=29 n(%)	Total N=56 n(%)
- Any primary system organ class			
- Total	3 (11.1)	2 (6.9)	5 (8.9)
Blood and lymphatic system disorders			
- Total	2 (7.4)	1 (3.4)	3 (5.4)
Thrombocytopenia	2 (7.4)	1 (3.4)	3 (5.4)
Psychiatric disorders			
- Total	1 (3.7)	1 (3.4)	2 (3.6)
Anxiety	1 (3.7)	0 (0.0)	1 (1.8)
Depression	0 (0.0)	1 (3.4)	1 (1.8)

- Primary system organ classes are presented alphabetically, preferred terms are sorted within primary organ
 class in descending frequency, as reported in the column*.
- A patient with multiple occurrences of an DLTs under one treatment is counted only once in the AE ca that
 treatment.
- A patient with multiple DLTs within a primary system organ class is counted only once in the total

Secondary Outcome Result(s)

Summary of (A) ruxolitinib and (B) buparlisib pharmacokinetics (Pharmacokinetic Analysis Set)

A) Ruxolitinib pharmacokinetics

PK parameter		Dose level 1 N=15	Dose level 2* N=42	Dose level 3 N=3	Dose level 4 N=3
AUC_{last} (h*ng/mL)	N	12	24	3	2
	Mean (SD)	435 (165)	564 (195)	550 (112)	1040 (55.3)
	Median [range]	399 [218, 797]	510 [264, 950]	507 [466, 677]	1040 [1000, 1080]

C_{max} (ng/mL)	N	12	24	3	2
	Mean (SD)	136 (37.1)	189 (51.2)	231 (49.7)	383 (158)
	Median (range)	139 [77.3, 189]	178 [97.2, 293]	205 [199, 288]	383 [271, 494]
T_{max} (h)	N	12	24	3	2
	Median (range)	1.00 [0, 1.50]	1.00 [0.417, 2.05]	0.500 [0.500, 0.517]	1.50 [1.50, 1.50]

B) Buparlisib pharmacokinetics

PK parameter		Dose level 1 N=15	Dose level 2* N=42	Dose level 3 N=3	Dose level 4 N=3
AUC_{last} (h*ng/mL)	N	12	19	3	3
	Mean (SD)	3630 (1270)	3100 (1420)	5660 (1440)	4630 (738)
	Median (range)	3530 [2190, 6600]	3010 [563, 5670]	4900 [4760, 7320]	4650 [3890, 5360]
C_{max} (ng/mL)	N	12	19	3	3
	Mean (SD)	444 (160)	414 (208)	564 (185)	579 (319)
	Median (range)	416 [241, 724]	360 [113, 870]	485 [432, 776]	488 [315, 934
T_{max} (h)	N	12	19	3	3
	Median (range)	1.73 [0.50, 2.05]	1.00 [0.50, 24.0]	1.50 [1.00, 1.98]	2.00 [1.00, 4.1

*Maximum tolerated dose (MTD).

Dose level 1, ruxolitinib 10 mg bid/buparlisib 60 mg qd; dose level 2, ruxolitinib 15 mg bid/buparlisib 60 mg qd; dose level 3, ruxolitinib 15 mg bid/buparlisib 80 mg qd; dose level 4, ruxolitinib 20 mg bid/buparlisib 80 mg qd.

Summary of Safety

Safety Results

Frequent adverse events (> 10% cutoff for All grades Overall), regardless of study drug relationship, by preferred term and arm – Total (Safety set)

	JAK naïve ____N=33____		Prior JAK ____N=30____		Total ____N=63____	
Preferred term	**All grades n(%)**	**Grade 3/4 n(%)**	**All grades n(%)**	**Grade 3/4 n(%)**	**All grades n(%)**	**Grade 3/4 n(%)**
-Total	33 (100)	25 (75.8)	30 (100)	25 (83.3)	63 (100)	50 (79.4)
Thrombocytopenia	17 (51.5)	7 (21.2)	19 (63.3)	12 (40.0)	36 (57.1)	19 (30.2)
Anaemia	16 (48.5)	10 (30.3)	14 (46.7)	10 (33.3)	30 (47.6)	20 (31.7)
Diarrhoea	5 (15.2)	0	13 (43.3)	2 (6.7)	18 (28.6)	2 (3.2)
Pyrexia	3 (9.1)	1 (3.0)	12 (40.0)	4 (13.3)	15 (23.8)	5 (7.9)
Abdominal pain	4 (12.1)	0	10 (33.3)	1 (3.3)	14 (22.2)	1 (1.6)
Asthenia	4 (12.1)	1 (3.0)	9 (30.0)	2 (6.7)	13 (20.6)	3 (4.8)
Dyspnoea	5 (15.2)	2 (6.1)	8 (26.7)	1 (3.3)	13 (20.6)	3 (4.8)
Decreased appetite	4 (12.1)	0	9 (30.0)	2 (6.7)	13 (20.6)	2 (3.2)
Fatigue	3 (9.1)	0	9 (30.0)	0	12 (19.0)	0
Epistaxis	5 (15.2)	1 (3.0)	6 (20.0)	0	11 (17.5)	1 (1.6)
Cough	3 (9.1)	0	8 (26.7)	0	11 (17.5)	0
Dizziness	6 (18.2)	0	5 (16.7)	0	11 (17.5)	0
Anxiety	8 (24.2)	4 (12.1)	2 (6.7)	0	10 (15.9)	4 (6.3)
Pruritus	4 (12.1)	0	6 (20.0)	1 (3.3)	10 (15.9)	1 (1.6)
Oedema peripheral	2 (6.1)	0	8 (26.7)	0	10 (15.9)	0
Hyperglycaemia	5 (15.2)	1 (3.0)	4 (13.3)	2 (6.7)	9 (14.3)	3 (4.8)
Nausea	3 (9.1)	0	6 (20.0)	1 (3.3)	9 (14.3)	1 (1.6)
Upper respiratory tract infection	3 (9.1)	1 (3.0)	6 (20.0)	0	9 (14.3)	1 (1.6)
Night sweats	3 (9.1)	0	6 (20.0)	0	9 (14.3)	0
Arthralgia	6 (18.2)	1 (3.0)	2 (6.7)	0	8 (12.7)	1 (1.6)
Abdominal pain upper	4 (12.1)	0	4 (13.3)	0	8 (12.7)	0
Urinary tract infection	6 (18.2)	0	2 (6.7)	0	8 (12.7)	0
Pneumonia	4 (12.1)	2 (6.1)	3 (10.0)	2 (6.7)	7 (11.1)	4 (6.3)
Hypertension	6 (18.2)	3 (9.1)	1 (3.3)	0	7 (11.1)	3 (4.8)
Depression	4 (12.1)	1 (3.0)	3 (10.0)	1 (3.3)	7 (11.1)	2 (3.2)
Constipation	3 (9.1)	0	4 (13.3)	0	7 (11.1)	0
Haematoma	5 (15.2)	0	2 (6.7)	0	7 (11.1)	0
Oropharyngeal pain	3 (9.1)	0	4 (13.3)	0	7 (11.1)	0
Vomiting	2 (6.1)	0	5 (16.7)	0	7 (11.1)	0

- Preferred terms are sorted in descending frequency, as reported in column labeled ‘Total’.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events is counted only once in the total row.
- Adverse events occurring more than 30 days after the discontinuation of study treatment are not summarized.

All deaths by preferred term and arm – Total (Safety set)

Primary cause of death Preferred term	JAK naïve N=33 n(%)	Prior JAK N=30 n(%)	Total N=63 n(%)
Total	3 (9.1)	4 (13.3)	7 (11.1)
Study indication	0 (0.0)	0 (0.0)	0 (0.0)
Other	3 (9.1)	4 (13.3)	7 (11.1)
Acute myeloid leukaemia	0 (0.0)	1 (3.3)	1 (1.6)
Haemorrhage intracranial	0 (0.0)	1 (3.3)	1 (1.6)
Multiple organ dysfunction syndrome	0 (0.0)	1 (3.3)	1 (1.6)
Myeloid leukaemia	0 (0.0)	1 (3.3)	1 (1.6)
Cardiac failure congestive	1 (3.0)	0 (0.0)	1 (1.6)
Duodenal ulcer haemorrhage	1 (3.0)	0 (0.0)	1 (1.6)
Leukaemia	1 (3.0)	0 (0.0)	1 (1.6)

- Preferred terms are sorted in descending frequency as reported in column labeled as 'Total'.
- All deaths during the study are included.

Serious adverse events, regardless of study drug relationship, by preferred term and arm – Total (Safety set)

	JAK naïve N=33		Prior JAK N=30		Total N=63	
Preferred term	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)
-Total	13 (39.4)	12 (36.4)	14 (46.7)	13 (43.3)	27 (42.9)	25 (39.7)
Pyrexia	1 (3.0)	1 (3.0)	4 (13.3)	4 (13.3)	5 (7.9)	5 (7.9)
Pneumonia	2 (6.1)	2 (6.1)	3 (10.0)	2 (6.7)	5 (7.9)	4 (6.3)
Acute myeloid leukaemia	1 (3.0)	1 (3.0)	2 (6.7)	2 (6.7)	3 (4.8)	3 (4.8)
Dyspnoea	1 (3.0)	1 (3.0)	1 (3.3)	1 (3.3)	2 (3.2)	2 (3.2)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	2 (6.7)	2 (6.7)	2 (3.2)	2 (3.2)
Thrombocytopenia	1 (3.0)	1 (3.0)	1 (3.3)	1 (3.3)	2 (3.2)	2 (3.2)
C-reactive protein increased	0 (0.0)	0 (0.0)	2 (6.7)	1 (3.3)	2 (3.2)	1 (1.6)
Acute pulmonary oedema	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Adverse drug reaction	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Anaemia	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Anxiety	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Cardiac failure congestive	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Cerebral haematoma	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Cerebrovascular accident	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Chills	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Clostridium difficile infection	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Corneal abscess	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)

	JAK naïve N=33		Prior JAK N=30		Total N=63	
Preferred term	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)	All grades n(%)	Grade 3/4 n(%)
Craniocerebral injury	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Cystitis	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Decreased appetite	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Diarrhoea	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Duodenal ulcer haemorrhage	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Epistaxis	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Generalised oedema	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Gout	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Herpes zoster	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Hyperglycaemia	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Interstitial lung disease	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Memory impairment	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Muscular weakness	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Oedema mucosal	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Osteomyelitis	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Palpitations	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Quality of life decreased	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Renal impairment	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Salmonellosis	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Sepsis	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Splenic rupture	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Squamous cell carcinoma	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Subdural haematoma	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Transfusion reaction	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Traumatic intracranial haemorrhage	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Tumour lysis syndrome	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Upper gastrointestinal haemorrhage	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Upper respiratory tract infection	1 (3.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
Vital capacity decreased	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	1 (1.6)	1 (1.6)
Abdominal distension	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Angina pectoris	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Arthritis bacterial	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.6)	0 (0.0)
Fluid overload	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.6)	0 (0.0)
Infection	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.6)	0 (0.0)
Organic brain syndrome	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	1 (1.6)	0 (0.0)

- Preferred terms are sorted in descending frequency, as reported in column labeled as ‘Total’.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events is counted only once in the total row.
- Adverse events occurring more than 30 days after the discontinuation of study treatment are not summarized.

Other Relevant Findings

Not applicable

Conclusion:

This was a phase Ib, open-label, multi-center, two-arm, dose-finding study to assess the safety and efficacy of the oral combination of ruxolitinib (INC424) and buparlisib (BKM120) in subjects with PMF, PPV-MF, or PET-MF.
The study enrolled 63 subjects (33 in the JAK naive arm, 30 in the Prior JAK arm), and five DLTs were observed (two at the MTD in the JAK naive arm). The DLTs observed at the MTD were grade 4 thrombocytopenia and grade 3 anxiety, both of which were suspected to be related to the study drug. Both DLTs were managed with dose adjustment or temporary interruption, and the thrombocytopenia DLT was additionally managed with concomitant medications. The MTD and RPIID was determined to be INC424 15 mg BID + BKM120 60 mg QD for both the JAK naive and Prior JAK arms.
The majority of subjects in both treatment arms had a decreased spleen length in the best percentage change from baseline and decreased change from baseline spleen volume regardless of MF type.
The descriptive analysis of PK parameters did not reveal any impact of buparlisib on the PK of ruxolitinib.
The most frequently reported AE across the treatment arms was thrombocytopenia. The frequency of thrombocytopenia of any grade was similar between the treatment arms, but the frequency of grade 3/4 thrombocytopenia was higher in the Prior JAK arm compared to the JAK naive arm.
A total of seven deaths were reported in the study.
The benefit/risk assessment of the combined treatment was not supportive for MF patients (although there was some evidence of improved spleen response in ruxolitinib + buparlisib combination treatments versus ruxolitinib monotherapy, there was unfavorable increased toxicity), which contributed to the decision to terminate the study early. Additionally, considering study results in different indications, particularly in the large Phase III studies in breast cancer and the manageable but challenging safety profile of buparlisib, Novartis made the decision not to pursue further development of buparlisib.

Date of Clinical Trial Report

13 Jun 2018