Sponsor
Novartis

Generic Drug Name
Imatinib, Buparlisib

Trial Indication(s)
Gastrointestinal stromal tumor

Protocol Number
CSTI571X2101

Protocol Title

A multi-arm dose-finding phase Ib multicenter study of imatinib in combination with the oral phosphatidyl-inositol 3-kinase (PI3-K) inhibitor BKM120 in patients with gastrointestinal stromal tumor (GIST) who failed prior therapy with imatinib and sunitinib.

Clinical Trial Phase
Phase IB

Phase of Drug Development

STI571 (imatinib): development phase IV; BKM120 (buparsilib): development phase III

Study Start/End Dates

Study Start Date: 19-Apr-2012 (first patient first visit)
Study Completion Date: 28-Jul-2016 (last patient last visit)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

Multi-center, open-label, multi-arm, Phase Ib; dose-finding study to investigate the feasibility of the combination of imatinib 400 mg with buparlisib in patients with histologically confirmed metastatic and/or unresectable GIST, who failed prior therapy with imatinib and sunitinib. The study was conducted in two stages: a dose-escalation part to establish the Maximum Tolerated Dose (MTD) and/or Recommended Phase II dose (RP2D), using daily doses of buparlisib (planned: [30 mg], 40 mg, 60 mg, 80 mg, and 100 mg, but actually used: 40 mg, 50 mg, 70 mg, 80 mg, and 100 mg), and a dose-expansion part at the MTD or RP2D.

Centers

11 centers in 8 countries: Belgium (1), Canada (1), France (2), Japan (1), Spain (1),The Netherlands (1), United Kingdom (2), United States (2).

Objectives:

Primary objective(s)
Primary Objective: to determine the MTD and/or a RP2D of buparlisib when administered in combination with imatinib 400 mg once daily.

Secondary objective(s)

- To assess the safety and tolerability profile of imatinib and buparlisib administered in combination.
- To evaluate the effect of imatinib on steady-state Pharmacokinetics (PK) of buparlisib and effect of buparlisib on steady-state PK of imatinib when co-administered.
- To characterize the steady-state PK profiles of imatinib and buparlisib when administered in combination.

- To perform a preliminary assessment of the clinical activity of imatinib and buparlisib combination treatment in patients with advanced GIST.

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

The study was conducted in two stages: a dose-escalation part to establish the MTD and/or RP2D, using daily doses of buparlisib (40 mg, 50 mg, 70 mg, 80 mg, and 100 mg), and a dose-expansion part at the MTD or RP2D.

During the *dose-escalation part* of the study, successive cohorts received increasing doses of buparlisib (40 mg, 50 mg, 70 mg, 80 mg, and 100 mg) with imatinib 400 mg daily.
In the *dose-expansion part*, a subset of patients received monotherapy with either imatinib or buparlisib for the first eight days of treatment and initiated the combination therapy on Day 9. The remaining patients were treated with the combination therapy starting on Day 1, buparlisib 80 mg and imatinib 400 mg once daily.

Statistical Methods The anti-tumor activity of the study combination was primarily evaluated based on patients in the dose-expansion part. Preliminary efficacy was assessed based on the Clinical Benefit Rate (CBR), defined as the proportion of patients with the best overall response of CR (Complete Response) or PR (Partial response); or a response of stable disease or better which lasts for at least 16 weeks after the start of study treatment. The response (CR or PR) must be a confirmed response at least 28 days after first evaluation of response.
Other efficacy variables considered were: Overall Response Rate (ORR), defined as the rate of patient with the best overall response of CR or PR (confirmed); Disease Control Rate (DCR), defined as the proportion of patients with the best overall response of CR or PR, or a response of stable disease or better >6 weeks after the start of study treatment (but before progression); and PFS (Progression Free Survival), defined as the time from the date of first study treatment to the date of first documented disease progression or date of death due to any cause, whichever occurs first. If a patient has not had an event, PFS is censored at the date of last adequate tumor assessment. The CBR, ORR, and DCR rates were summarized with the 95% confidence intervals (CIs) using exact Pearson-Clopper limits. PFS was estimated using the Kaplan-Meier method. The efficacy variables were evaluated based on the FAS (Full Analysis Set).
The assessment of safety was based mainly on the type, frequency and severity of AEs (Adverse Event). Summaries of AEs, SAEs (Serious Adverse Event), and deaths were based on the safety set and focused on the on-treatment period. AEs were to be followed for 30 days from the last dose. Information regarding AEs was collected and coded using the MedDRA (Medical Dictionary

for Regulatory Activities) Version 19.0 available at time of reporting, while Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 was used for grading the severity at every visit.
Planned statistical analyses for pharmacokinetic (PK) data (secondary objectives) were not performed.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

1. Male or female patients ≥ 18 years of age
2. World Health Organization (WHO) performance status (PS) of 0-2
3. Histologically confirmed diagnosis of GIST that is unresectable or metastatic
4. Available tissue specimen:
   - Dose-escalation cohorts: patients must have available archival tumor tissue which can be shipped during the course of the study
   - Dose-expansion cohort: patients must have available archival tumor tissue which can be shipped during the course of the study and must agree to a fresh pre-treatment biopsy.
5. Failed prior therapy with imatinib followed by sunitinib for the treatment of unresectable or metastatic GIST. Note the following specific criteria for the two phases of the trial:
   - Dose-escalation cohorts: patients who failed prior therapy with imatinib and then have failed therapy with sunitinib. Treatment failure may be due to either disease progression on therapy (both imatinib and sunitinib) or intolerance to therapy (sunitinib). Dose-escalation cohort patients may have had additional lines of therapy not limited to imatinib and sunitinib.
   - Dose-expansion cohort: patients must have documented disease progression on both imatinib and sunitinib. In addition, patients may have had no more than two lines of prior therapy (i.e. treatment with imatinib followed by treatment with sunitinib).
   - Adjuvant imatinib will not count as a prior course of imatinib for the purposes of this criterion

Exclusion Criteria:

1. Previous treatment with PI3-K inhibitors
2. A medical history of any of the following mood disorders as judged by the Investigator or a psychiatrist:

- Medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or thoughts, or homicidal thoughts (immediate risk of doing harm to others)
- ≥ Common Terminology Criteria for Adverse Events (CTCAE) grade 3 anxiety

3. When completing the patient questionnaires at screening:
   - Meets the cut-off score of ≥ 10 in the nine item depression scale of the Patient Health Questionnaire (PHQ-9) or a cut-off of ≥ 15 in the Generalized Anxiety Disorder Assessment (GAD 7) mood scale respectively, or
   - Selects positive response of 1, 2, 3 to question number 9 regarding potential for suicidal thoughts or ideation in the PHQ-9 (independent of the total score of the PHQ-9)
4. Severe and/or uncontrolled concurrent medical condition that, in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. acute or chronic liver, pancreatic, severe renal disease considered unrelated to study disease, chronic pulmonary disease including dyspnea at rest from any cause).
5. Poorly controlled diabetes mellitus (defined as HbA1c > 8%)

Participant Flow Table

Analysis sets by treatment group (FAS)

Disposition	Buparlisib daily dose (+ Imatinib 400 mg)					All patients
Reason	40 mg N=4 n (%)	50 mg N=4 n (%)	70 mg N=3 n (%)	80 mg N=43 n (%)	100 mg N=6 n (%)	N=60 n (%)
Patients treated						
Treatment ended	4 (100)	4 (100)	3 (100)	43 (100)	6 (100)	60 (100)
Primary reason for end of treatment						
Progressive disease[1]	3 (75.0)	3 (75.0)	3 (100)	34 (79.1)	4 (66.7)	47 (78.3)
Adverse event	0	1 (25.0)	0	7 (16.3)	2 (33.3)	10 (16.7)
Subject/guardian decision	1 (25.0)	0	0	2 (4.7)	0	3 (5.0)

FAS = full analysis set.
[1] Not applicable to patients in the dose-expansion part who discontinued during the 8-day monotherapy PK run-in.
Percentage is based on N.

Baseline Characteristics

Demographics by treatment group (FAS)

Variable	Buparlisib daily dose (+ Imatinib 400 mg)					All patients
	40 mg N=4	50 mg N=4	70 mg N=3	80 mg N=43	100 mg N=6	N=60
Age (years)						
Mean (SD)	45.8 (18.30)	52.8 (7.85)	65.7 (11.24)	56.7 (11.96)	60.5 (11.24)	56.5 (12.31)
Median (Range)	40.5 (30-72)	52.0 (44-63)	63.0 (56-78)	57.0 (28-78)	63.5 (42-72)	56.5 (28-78)
Age category (years) n (%)						
<65	3 (75.0)	4 (100)	2 (66.7)	31 (72.1)	3 (50.0)	43 (71.7)
≥ 65	1 (25.0)	0	1 (33.3)	12 (27.9)	3 (50.0)	17 (28.3)
Sex n (%)						
Male	2 (50.0)	2 (50.0)	3 (100)	27 (62.8)	5 (83.3)	39 (65.0)
Female	2 (50.0)	2 (50.0)	0	16 (37.2)	1 (16.7)	21 (35.0)
Race n (%)						
Caucasian	4 (100)	4 (100)	3 (100)	39 (90.7)	6 (100)	56 (93.3)
Asian	0	0	0	3 (7.0)	0	3 (5.0)
Black	0	0	0	1 (2.3)	0	1 (1.7)
Ethnicity n (%)						
Hispanic or Latino	0	1 (25.0)	1 (33.3)	5 (11.6)	0	7 (11.7)
Japanese	0	0	0	2 (4.7)	0	2 (3.3)
Chinese	0	0	0	1 (2.3)	0	1 (1.7)
Not reported	0	0	0	6 (14.0)	1 (16.7)	7 (11.7)
Other	4 (100)	3 (75.0)	2 (66.7)	27 (62.8)	5 (83.3)	41 (68.3)
Unknown	0	0	0	2 (4.7)	0	2 (3.3)
Height (cm)						
Mean (SD)	179.00 (11.136)	169.75 (5.560)	177.57 (7.865)	171.16 (8.703)	173.90 (9.085)	172.18 (8.774)
Median (Range)	177.0 (168.0-194.0)	170.0 (163.0-176.0)	177.0 (170.0-185.7)	171.0 (152.1-192.0)	174.0 (163.0-189.0)	172.0 (152.1-194.0)
Weight (kg)[1]						
Mean (SD)	64.13 (21.182)	92.73 (20.408)	91.97 (5.604)	75.15 (16.565)	79.08 (10.545)	76.82 (17.092)

Variable	Buparlisib daily dose (+ Imatinib 400 mg)					All patients
	40 mg N=4	50 mg N=4	70 mg N=3	80 mg N=43	100 mg N=6	N=60
Median (Range)	63.15 (40.2-90.0)	95.25 (66.4-114.0)	95.00 (85.5-95.4)	76.70 (43.6-109.0)	82.70 (62.0-88.8)	77.50 (40.2-114.0)
Body surface area (m^2)						
Mean (SD)	1.78 (0.352)	2.11 (0.274)	2.14 (0.085)	1.89 (0.240)	1.97 (0.163)	1.92 (0.246)
Median (Range)	1.77 (1.4-2.2)	2.14 (1.8-2.4)	2.14 (2.1-2.2)	1.95 (1.4-2.3)	2.03 (1.7-2.1)	1.97 (1.4-2.4)
Body mass index (kg/m^2)						
Mean (SD)	19.59 (4.200)	31.91 (5.122)	29.27 (3.120)	25.58 (5.270)	26.16 (3.143)	25.85 (5.382)
Median (Range)	20.10 (14.2-23.9)	32.92 (25.0-36.8)	27.66 (27.3-32.9)	25.49 (16.3-41.0)	25.66 (23.3-29.7)	25.52 (14.2-41.0)
ECOG Performance status, n (%)[1]						
0	0	2 (50.0)	3 (100)	24 (55.8)	4 (66.7)	33 (55.0)
1	4 (100)	2 (50.0)	0	18 (41.9)	2 (33.3)	26 (43.3)
2	0	0	0	1 (2.3)	0	1 (1.7)

ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; SD = standard deviation.
[1] Weight and ECOG performance status were the last non-missing values prior to first dose of study treatment.
Body mass index: weight[kg]/(height[m]^2)
Body surface area: 234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000 (Gehan and George's formula)

Summary of Efficacy

Efficacy Outcome Result(s)

Best overall response per Investigator review (FAS; Dose-expansion part)

	All patients N=35	
	n (%)	**[95% CI] [1]**
Best overall response		
Complete Response (CR)	0	_
Partial Response (PR)	0	_
Stable Disease (SD)	19 (54.3)	_
Progressive Disease (PD)	14 (40.0)	_
Unknown	2 (5.7)	_
Clinical Benefit Rate (CBR): CR+PR+SD ≥ 16 weeks	10 (28.6)	[14.6, 46.3]
Overall Response Rate (ORR): CR+PR	0	[0, 10.0]
Disease Control Rate (DCR): CR+PR+SD >6 weeks	19 (54.3)	[36.6, 71.2]

CI = confidence interval; FAS = full analysis set.
[1] The 95% CI for the frequency distribution of each variable were computed using the Clopper-Pearson method.

Analysis of progression-free survival as per Investigator using Kaplan-Meier method (FAS; Dose-expansion part)

	All patients N=35
Number of events - n (%)	29 (82.9)
Progression	27 (77.1)
Death	2 (5.7)
Number of censoring - n (%)	6 (17.1)
Percentiles (95% CI) (months)	
25th	1.9 (1.7, 1.9)
50th	3.5 (1.9, 5.4)
75th	5.5 (3.7, 11.4)
% Event-free probability estimates (95% CI)	
2 months	57.4 (38.8, 72.2)
4 months	37.3 (20.8, 53.8)
6 months	22.4 (9.4, 38.7)
8 months	18.6 (7.0, 34.6)
11 months	11.2 (2.9, 25.8)

CI = confidence interval; FAS = full analysis set.
Percentiles (in months) with 95% CIs were calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
% Event-free probability estimate was the estimated probability that a patient remained event-free for the specified time point and was obtained from the Kaplan-Meier survival estimates; Kalbfleisch and Prentice (1980) method was used for CIs of Kaplan-Meier estimates.

Summary of Safety

Safety Results

Overview of dose escalation teleconferences (Dose-determining set)

Dose escalation teleconference (in combination with imatinib 400 mg daily)	# evaluable patients	Dose Limiting Toxicities (DLTs) in cycle 1 (up to 28 days of dosing), Preferred term	Decision
1. BKM 40 mg (23-July-2012)	4	0	Go to BKM 50 mg
2. BKM 50 mg (04-Oct-2012)	4	1 patient - Anaphylactic reaction	Go to BKM 70 mg
3. BKM 70 mg (04-Dec-2012)	3	0	Go to BKM 80 mg
4. BKM 80 mg (07-Feb-2013)	4	0	Go to BKM 100 mg
5. BKM 100 mg (12-Jun-2013)	6	3 patients: - Stomatitis - Hyperglycaemia - Depression	Go to BKM 80 mg
6. BKM 80 mg (04-Sep-2013)	4	0	Declare MTD at BKM 80 mg

Adverse Events by System Organ Class (Safety set)

Adverse events, regardless of study treatment relationship, by primary system organ class, maximum grade, and treatment group (at least 10% in all grade patients, Safety set)

Primary SOC	Buparlisib daily dose (+ Imatinib 400 mg)										All patients	
	40 mg N=4		50 mg N=4		70 mg N=3		80 mg N=43		100 mg N=6		N=60	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	4 (100)	2 (50.0)	4 (100)	2 (50.0)	3 (100)	1 (33.3)	43 (100)	29 (67.4)	6 (100)	5 (83.3)	60 (100)	39 (65.0)
Blood and lymphatic system disorders	0	0	1 (25.0)	0	1 (33.3)	0	13 (30.2)	3 (7.0)	3 (50.0)	0	18 (30.0)	3 (5.0)
Ear and labyrinth disorders	0	0	0	0	1 (33.3)	0	6 (14.0)	0	0	0	7 (11.7)	0
Eye disorders	0	0	0	0	1 (33.3)	0	15 (34.9)	0	0	0	16 (26.7)	0
Gastrointestinal disorders	3 (75.0)	0	3 (75.0)	1 (25.0)	3 (100)	0	38 (88.4)	10 (23.3)	5 (83.3)	1 (16.7)	52 (86.7)	12 (20.0)
General disorders and administration site condition	2 (50.0)	0	2 (50.0)	0	2 (66.7)	0	33 (76.7)	4 (9.3)	4 (66.7)	1 (16.7)	43 (71.7)	5 (8.3)
Infections and infestations	0	0	0	0	1 (33.3)	0	11 (25.6)	1 (2.3)	0	0	12 (20.0)	1 (1.7)
Investigations	1 (25.0)	0	1 (25.0)	0	3 (100)	1 (33.3)	21 (48.8)	7 (16.3)	2 (33.3)	1 (16.7)	28 (46.7)	9 (15.0)
Metabolism and nutrition disorders	1 (25.0)	1 (25.0)	2 (50.0)	0	2 (66.7)	0	27 (62.8)	8 (18.6)	5 (83.3)	3 (50.0)	37 (61.7)	12 (20.0)
Musculoskeletal and connective tissue disorders	3 (75.0)	0	3 (75.0)	0	1 (33.3)	0	15 (34.9)	1 (2.3)	4 (66.7)	0	26 (43.3)	1 (1.7)
Nervous system disorders	2 (50.0)	0	1 (25.0)	0	1 (33.3)	0	20 (46.5)	3 (7.0)	3 (50.0)	0	27 (45.0)	3 (5.0)
Psychiatric disorders	2 (50.0)	0	0	0	1 (33.3)	1 (33.3)	19 (44.2)	0	3 (50.0)	2 (33.3)	25 (41.7)	3 (5.0)
Renal and urinary disorders	0	0	0	0	1 (33.3)	0	5 (11.6)	1 (2.3)	0	0	6 (10.0)	1 (1.7)
Respiratory, thoracic and mediastinal disorders	0	0	2 (50.0)	0	1 (33.3)	0	7 (16.3)	0	2 (33.3)	2 (33.3)	12 (20.0)	2 (3.3)
Skin and subcutaneous tissue disorders	0	0	1 (25.0)	0	2 (66.7)	0	22 (51.2)	7 (16.3)	6 (100)	1 (16.7)	31 (51.7)	8 (13.3)

Primary SOC	Buparlisib daily dose (+ Imatinib 400 mg)										All patients	
	40 mg N=4		50 mg N=4		70 mg N=3		80 mg N=43		100 mg N=6		N=60	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Vascular disorders	0	0	1 (25.0)	0	1 (33.3)	0	7 (16.3)	2 (4.7)	1 (16.7)	0	10 (16.7)	2 (3.3)

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA= Medical Dictionary for Regulatory Activities; SOC = system organ class.
Primary system organ classes are presented alphabetically. A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.
A patient with multiple adverse events was counted only once in the total row.
MedDRA Version 19.0; CTCAE Version 4.03 (without CTCAE grade 5).

Most Frequently Reported AEs Overall by Preferred Term n (%)

Adverse events, regardless of study treatment relationship, by preferred term, maximum grade and treatment group (greater than 10% in all grade patients; Safety set)

Primary system organ class	Buparlisib daily dose (+ Imatinib 400 mg)										All patients	
	40 mg N=4		50 mg N=4		70 mg N=3		80 mg N=43		100 mg N=6		N=60	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	4 (100)	2 (50.0)	4 (100)	2 (50.0)	3 (100)	1 (33.3)	43 (100)	29 (67.4)	6 (100)	5 (83.3)	60 (100)	39 (65.0)
Nausea	1 (25.0)	0	3 (75.0)	0	2 (66.7)	0	27 (62.8)	1 (2.3)	5 (83.3)	0	38 (63.3)	1 (1.7)
Fatigue	2 (50.0)	0	1 (25.0)	0	2 (66.7)	0	21 (48.8)	1 (2.3)	3 (50.0)	0	29 (48.3)	1 (1.7)
Diarrhoea	2 (50.0)	0	0	0	2 (66.7)	0	20 (46.5)	2 (4.7)	3 (50.0)	1 (16.7)	27 (45.0)	3 (5.0)
Decreased appetite	1 (25.0)	1 (25.0)	2 (50.0)	0	1 (33.3)	0	11 (25.6)	2 (4.7)	2 (33.3)	0	17 (28.3)	3 (5.0)
Hyperglycaemia	0	0	1 (25.0)	0	1 (33.3)	0	10 (23.3)	0	5 (83.3)	2 (33.3)	17 (28.3)	2 (3.3)
Abdominal pain	0	0	2 (50.0)	1 (25.0)	0	0	11 (25.6)	1 (2.3)	2 (33.3)	0	15 (25.0)	2 (3.3)
Anaemia	0	0	1 (25.0)	0	1 (33.3)	0	11 (25.6)	1 (2.3)	2 (33.3)	0	15 (25.0)	1 (1.7)
Rash	0	0	0	0	1 (33.3)	0	11 (25.6)	3 (7.0)	2 (33.3)	1 (16.7)	14 (23.3)	4 (6.7)
Insomnia	1 (25.0)	0	0	0	1 (33.3)	0	9 (20.9)	0	1 (16.7)	1 (16.7)	12 (20.0)	1 (1.7)
Vomiting	2 (50.0)	0	1 (25.0)	0	0	0	6 (14.0)	0	3 (50.0)	0	12 (20.0)	0
Aspartate aminotransferase increased	0	0	1 (25.0)	0	1 (33.3)	0	9 (20.9)	1 (2.3)	0	0	11 (18.3)	1 (1.7)
Pruritus	0	0	0	0	1 (33.3)	0	10 (23.3)	0	0	0	11 (18.3)	0
Asthenia	0	0	1 (25.0)	0	0	0	8 (18.6)	2 (4.7)	1 (16.7)	1 (16.7)	10 (16.7)	3 (5.0)
Constipation	0	0	0	0	2 (66.7)	0	8 (18.6)	1 (2.3)	0	0	10 (16.7)	1 (1.7)
Oedema peripheral	0	0	2 (50.0)	0	0	0	8 (18.6)	0	0	0	10 (16.7)	0
Anxiety	0	0	0	0	0	0	8 (18.6)	0	1 (16.7)	0	9 (15.0)	0
Blood creatinine increased	1 (25.0)	0	0	0	0	0	7 (16.3)	1 (2.3)	1 (16.7)	0	9 (15.0)	1 (1.7)
Hypokalaemia	0	0	0	0	0	0	7 (16.3)	3 (7.0)	2 (33.3)	0	9 (15.0)	3 (5.0)
Back pain	1 (25.0)	0	1 (25.0)	0	0	0	6 (14.0)	0	0	0	8 (13.3)	0
Depression	0	0	0	0	0	0	7 (16.3)	0	1 (16.7)	1 (16.7)	8 (13.3)	1 (1.7)

Primary system organ class	Buparlisib daily dose (+ Imatinib 400 mg)										All patients	
	40 mg N=4		50 mg N=4		70 mg N=3		80 mg N=43		100 mg N=6		N=60	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Muscle spasms	1 (25.0)	0	0	0	1 (33.3)	0	5 (11.6)	0	1 (16.7)	0	8 (13.3)	0
Periorbital oedema	0	0	0	0	1 (33.3)	0	7 (16.3)	0	0	0	8 (13.3)	0
Abdominal pain upper	0	0	1 (25.0)	0	1 (33.3)	0	5 (11.6)	2 (4.7)	0	0	7 (11.7)	2 (3.3)
Blood alkaline phosphatase increased	0	0	1 (25.0)	0	1 (33.3)	0	5 (11.6)	1 (2.3)	0	0	7 (11.7)	1 (1.7)
Dysgeusia	0	0	0	0	0	0	5 (11.6)	0	2 (33.3)	0	7 (11.7)	0
Headache	1 (25.0)	0	1 (25.0)	0	0	0	5 (11.6)	0	0	0	7 (11.7)	0
Hypertension	0	0	1 (25.0)	0	1 (33.3)	0	4 (9.3)	2 (4.7)	1 (16.7)	0	7 (11.7)	2 (3.3)
Weight decreased	0	0	0	0	2 (66.7)	0	4 (9.3)	1 (2.3)	1 (16.7)	0	7 (11.7)	1 (1.7)

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA= Medical Dictionary for Regulatory Activities; SOC = system organ class.
Preferred terms are sorted in descending frequency of all grades column, as reported in the All patients column. A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.

Serious Adverse Events and Deaths (Safety set)

Category	Buparlisib daily dose (+ Imatinib 400 mg)										All patients	
	40 mg N=4		50 mg N=4		70 mg N=3		80 mg N=43		100 mg N=6		N=60	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
All deaths[1]	2 (50.0)	-	1 (25.0)	-	0	-	7 (16.3)	-	2 (33.3)	-	12 (20.0)	-
On-treatment deaths[2]	0	-	0	-	0	-	3 (7.0)	-	0	-	3 (5.0)	-
Adverse events	4 (100)	2 (50.0)	4 (100)	2 (50.0)	3 (100)	1 (33.3)	43 (100)	29 (67.4)	6 (100)	5 (83.3)	60 (100)	39 (65.0)
Suspected to be drug-related	4 (100)	1 (25.0)	4 (100)	1 (25.0)	3 (100)	1 (33.3)	42 (97.7)	20 (46.5)	6 (100)	4 (66.7)	59 (98.3)	27 (45.0)
Serious adverse events	1 (25.0)	1 (25.0)	2 (50.0)	2 (50.0)	1 (33.3)	0	16 (37.2)	15 (34.9)	3 (50.0)	3 (50.0)	23 (38.3)	21 (35.0)
Suspected to be drug-related	0	0	1 (25.0)	1 (25.0)	0	0	5 (11.6)	5 (11.6)	2 (33.3)	2 (33.3)	8 (13.3)	8 (13.3)
AEs leading to discontinuation	0	0	1 (25.0)	1 (25.0)	1 (33.3)	0	9 (20.9)	6 (14.0)	2 (33.3)	2 (33.3)	13[3] (21.7)	9 (15.0)
Suspected to be drug-related	0	0	1 (25.0)	1 (25.0)	0	0	6 (14.0)	4 (9.3)	2 (33.3)	2 (33.3)	9 (15.0)	7 (11.7)
AEs requiring dose interruption and/or change	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	1 (33.3)	1 (33.3)	32 (74.4)	17 (39.5)	3 (50.0)	1 (16.7)	38 (63.3)	21 (35.0)
Suspected to be drug-related	0	0	0	0	1 (33.3)	1 (33.3)	28 (65.1)	14 (32.6)	3 (50.0)	1 (16.7)	32 (53.3)	16 (26.7)
AEs requiring additional therapy	4 (100)	1 (25.0)	4 (100)	2 (50.0)	3 (100)	1 (33.3)	41 (95.3)	22 (51.2)	6 (100)	3 (50.0)	58 (96.7)	29 (48.3)
Suspected to be drug-related	3 (75.0)	1 (25.0)	3 (75.0)	1 (25.0)	1 (33.3)	1 (33.3)	37 (86.0)	13 (30.2)	5 (83.3)	2 (33.3)	49 (81.7)	18 (30.0)

[1] All deaths including those >30 days after end of treatment.
[2] Deaths occurring >30 days after end of treatment are not included.

Other Relevant Findings

Not Applicable

Conclusion:

All results related to safety of the drug need to be interpreted with caution as the sample size is very small in each treatment group. The enrolled study population consisted of patients with advanced GIST, and as expected the patients had associated comorbid conditions. Overall, the safety profile of buparlisib when administered in combination with imatinib was found acceptable. The MTD was declared at buparlisib 80 mg in combination with imatinib 400 mg once daily in the dose-escalation part and four patients reported DLTs during the dose-escalation part of the study. The results of this study did demonstrate clinical activity in terms of PFS (e.g. results from the "RIGHT" study in advanced GIST patients treated with imatinib rechallenge after previous progression on imatinib and sunitinib showed a median PFS of 1.8 months). However, the results for the combination therapy in this study did not appear to be sufficiently different compared to those observed with approved third line monotherapy for advanced GIST such as regorafenib (median PFS: 3.5 months for buparlisib + 400 mg imatinib versus 4.8 months for regorafenib). Furthermore, it did not show improvement on ORR (CR+PR) (0% versus 4.5%) and stable disease rate (54.3% versus 71.4%) for the combination therapy versus regorafenib, respectively.

The safety profile of buparlisib in this study was consistent with the previously known safety profile.

Limited efficacy was noted in advanced GIST patients. Given the limited activity, the benefit-risk balance does not favor the use of this combination in this population. Further development of this combination therapy (buparlisib + 400 mg imatinib) is not recommended in the treatment of patients with third/fourth line advanced/metastatic GIST.

Date of Clinical Trial Report

24 April 2017