NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Imatinib and alpelisib

Trial Indication(s)

Gastrointestinal stromal tumor

Protocol Number

CSTI571X2103

Protocol Title

A dose-finding phase Ib multicenter study of imatinib in combination with the oral phosphatidyl-inositol 3-kinase (PI3K) inhibitor BYL719 in patients with gastrointestinal stromal tumor (GIST) who failed prior therapy with imatinib and sunitinib

Clinical Trial Phase

Phase 1

Phase of Drug Development

STI571 (imatinib): Phase IV; BYL719 (alpelisib): Phase IV

Study Start/End Dates

Study Start Date: February 2013 (Actual)
Primary Completion Date: October 2018 (Actual)
Study Completion Date: October 2018 (Actual)

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was an open-label, Phase Ib, dose-finding study in which safety and tolerability of escalating doses of alpelisib in combination with imatinib administered at a dose of 400 mg once daily in subjects with metastatic and/or unresectable GIST, who failed prior therapy with imatinib and sunitinib, were investigated.

The study was conducted in two parts. During the dose-escalation part, successive cohorts of subjects had a run-in period of 7 days receiving imatinib monotherapy at 400 mg daily, then received increasing doses of alpelisib (200 mg, 250 mg, 350 mg) in combination with imatinib 400 mg daily until maximum tolerated dose (MTD) and rapid phase 2 dose (RP2D) was determined. A Bayesian Logistic Regression Model (BLRM) with the escalation with overdose control (EWOC) was used.

Once the MTD and/or RP2D was established, approximately 35 subjects were enrolled into the dose expansion part of the study, treated with the combination therapy starting on Day 1, alpelisib 350 mg and imatinib 400 mg once daily.

Centers

11 centers in 8 countries: Spain(1), United States(1), France(1), Netherlands(2), Italy(2), Belgium(1), United Kingdom(1), Germany(2)

Objectives:

Primary objective:

To determine the MTD and/or a RP2D of alpelisib when administered orally in combination with imatinib 400 mg (once daily) as measured by the frequency and characteristics of dose limiting toxicities (DLTs).

Secondary objectives:

- Assess the safety and tolerability profile of imatinib and alpelisib administered in combination measured by the frequency and characteristics of DLTs and type, frequency and severity of adverse drug reactions.
- Assess the clinical activity of imatinib and alpelisib combination treatment in subjects with advanced GIST by measuring clinical benefit rate (CBR).

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

Film coated tablets of imatinib for oral administration were supplied to the Investigators at dose strengths of 100 mg and 400 mg. Alpelisib tablets for oral administration were supplied to the Investigators at dose strengths of 50 mg and 200 mg.

Statistical Methods

MTD/RP2D: Estimation of MTD and/or RP2D in the dose-escalation phase of the study was based upon the estimation of the probability of DLTs. The DLTs were summarized based on dose determining set, by primary system organ class and preferred term for each dose cohort, and a summary of posterior distribution of DLT rates was also provided.

Efficacy: The CBR defined as confirmed CR or PR; or SD of at least 16 weeks was used to evaluate the preliminary efficacy of the combination therapy. Other efficacy variables including, disease control rate (DCR) (at 6 weeks) and progression free survival (PFS) were evaluated. Efficacy analyses were based on FAS. The CBR rate, ORR rate, and DCR rate was summarized with the 95% CIs using exact Pearson-Clopper limits, and PFS was estimated using the Kaplan-Meier method.

Summary – Results

A total of 56 subjects with advanced GIST were enrolled in the study. All subjects had discontinued study treatment, mainly due to progressive disease (64.3%).

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Male or female patients ≥ 18 years of age -WHO performance status (PS) of 0-2
- Histologically confirmed diagnosis of GIST that is unresectable or metastatic
-.Available tissue specimen:
• Dose-escalation part: subjects were required to have available archival tumor tissue which could be shipped during the course of the study. In the absence of archival tumor tissue, subjects were to agree to a fresh pre-treatment biopsy at Screening.
• Dose-expansion part: subjects must have had available archival tumor tissue which could be shipped during the course of the study and must have agreed to a fresh pre-treatment biopsy.
- Failed prior therapy with imatinib followed by sunitinib for the treatment of unresectable or metastatic GIST. Note the following specific criteria for the two parts of the trial:
• Dose-escalation part: patients who failed prior therapy with imatinib and then have failed therapy with sunitinib. Treatment failure may be due to either disease pro gression on therapy (both imatinib and sunitinib) or intolerance to therapy (sunitinib)

Dose- escalation part subjects could have had additional lines of therapy not limited to imatinib and sunitinib.
• Dose-expansion part: patients must have had documented disease progression on both imatinib and sunitinib. In addition, patients may have had up to three lines of prior therapy (i.e. treatment with imatinib and sunitinib and then may have received one other line of therapy). Note: Adjuvant imatinib did not count as a prior course of imatinib for the purposes of this criterion unless the patient had disease progression during adjuvant treatment.
- Radiological (CT/MRI) confirmation of disease progression (RECIST criteria) during prior therapy with imatinib and sunitinib will be required for patients entering the Dose-expansion part

Exclusion Criteria:
- Previous treatment with PI3K inhibitors
- Patient had active uncontrolled or symptomatic central nervous system (CNS) metastases
- 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.
- Patients with diabetes mellitus requiring insulin treatment and/or with clinical signs or with FPG >120mg/dL / 6.7mmol/L, or history of documented steroid-induced diabetes mellitus
- Patients who had not recovered to grade 1 or better from any adverse events related to previous imatinib and/or sunitinib therapy before screening procedures are initiated

Participant Flow Table

Overall Study

	BYL 200mg + STI 400mg	BYL 250mg + STI 400mg	BYL 350mg + STI 400mg	Total
Arm/Group Description	Subjects in this arm received 200 mg of BYL719 in combination with 400 mg imatinib daily	Subjects in this arm received 250 mg of BYL719 in combination with 400 mg imatinib daily	Subjects in this arm received 350 mg of BYL719 in combination with 400 mg imatinib daily	
Started	4	6	46	56
Completed	0	0	0	0
Not Completed	4	6	46	56

Progressive disease	2	5	29	36
Adverse Event	1	1	10	12
Subject/guardian decision	1	0	6	7
Death	0	0	1	1

Baseline Characteristics

	BYL 200mg + STI 400mg	BYL 250mg + STI 400mg	BYL 350mg + STI 400mg	Total
Arm/Group Description	Subjects in this arm received 200 mg of BYL719 in combination with 400 mg imatinib daily	Subjects in this arm received 250 mg of BYL719 in combination with 400 mg imatinib daily	Subjects in this arm received 350 mg of BYL719 in combination with 400 mg imatinib daily	
Number of Participants [units: participants]	4	6	46	56
Age Continuous (units: years) Mean ± Standard Deviation				
	61.0±11.40	53.7±12.88	57.2±11.32	57.1±11.37
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)				
Female	1	1	17	19
Male	3	5	29	37
Race/Ethnicity, Customized (units: Participants)				

Caucasian	4	6	43	53
Black	0	0	2	2
Pacific Islander	0	0	1	1

Summary of Efficacy

Primary Outcome Result(s)

Frequency of dose limiting toxicities (DLTs)

(Time Frame: 28 days (1st cycle))

	BYL 200mg + STI 400mg	BYL 250mg + STI 400mg	BYL 350mg + STI 400mg
Arm/Group Description	Subjects in this arm received 200 mg of BYL719 in combination with 400 mg imatinib daily	Subjects in this arm received 250 mg of BYL719 in combination with 400 mg imatinib daily	Subjects in this arm received 350 mg of BYL719 in combination with 400 mg imatinib daily
Number of Participants Analyzed [units: participants]	4	6	9
Frequency of dose limiting toxicities (DLTs) (units: participants)			
	1	0	2

Characteristics of dose limiting toxicities (DLTs)

(Time Frame: 28 days (1st cycle))

	BYL 200mg + STI 400mg	BYL 250mg + STI 400mg	BYL 350mg + STI 400mg

Arm/Group Description	Subjects in this arm received 200 mg of BYL719 in combination with 400 mg imatinib daily	Subjects in this arm received 250 mg of BYL719 in combination with 400 mg imatinib daily	Subjects in this arm received 350 mg of BYL719 in combination with 400 mg imatinib daily
Number of Participants Analyzed [units: participants]	4	6	9
Characteristics of dose limiting toxicities (DLTs) (units: participants) Count of Participants (Not Applicable)			
Investigatns: Aspartate aminotransferase increased	1 (25%)	0 (%)	0 (%)
Investigations: Blood bilirubin increased	1 (25%)	0 (%)	0 (%)
Investigations: Total	1 (25%)	0 (%)	0 (%)
Metabolism and nutrition disorders: hyperglycaemia	0 (%)	0 (%)	2 (22.22%)
Metabolism and nutrition disorders: Total	0 (%)	0 (%)	2 (22.22%)

Secondary Outcome Result(s)

Clinical benefit rate (CBR)

(Time Frame: 28 days (1st cycle))

Arm/Group Description	BYL 350mg + STI 400mg
	Subjects in this arm received 350

	mg of BYL719 in combination with 400 mg imatinib daily
Number of Participants Analyzed [units: participants]	35
Clinical benefit rate (CBR) (units: Participants) Count of Participants (Not Applicable)	
	9 (25.71%)

Overall response rate (ORR)

(Time Frame: 28 days (1st cycle))

	BYL 350mg + STI 400mg
Arm/Group Description	Subjects in this arm received 350 mg of BYL719 in combination with 400 mg imatinib daily
Number of Participants Analyzed [units: participants]	35
Overall response rate (ORR) (units: Participants) Count of Participants (Not Applicable)	
	1 (2.86%)

Disease control rate (DCR)

(Time Frame: 28 days (1st cycle))

	BYL 350mg + STI 400mg
Arm/Group Description	Subjects in this arm received 350 mg of BYL719 in combination with 400 mg imatinib daily
Number of Participants Analyzed [units: participants]	35
Disease control rate (DCR) (units: Participants) Count of Participants (Not Applicable)	
	16 (45.71%)

Progression free survival (PFS)

(Time Frame: approx. 33 months)

	BYL 350mg + STI 400mg
Arm/Group Description	Subjects in this arm received 350 mg of BYL719 in combination with 400 mg imatinib daily

Number of Participants Analyzed [units: participants]	35
Progression free survival (PFS) (units: Months) Median (95% Confidence Interval)	
	2.0 (1.8 to 4.6)

Summary of Safety

Safety Results

All-Cause Mortality

	BYL 200mg + STI 400mg N = 4	BYL 250mg + STI 400mg N = 6	BYL 350mg + STI 400mg N = 46	All@patients N = 56
Arm/Group Description	Subjects in this arm received 200 mg of BYL719 in combination with 400 mg imatinib daily	Subjects in this arm received 250 mg of BYL719 in combination with 400 mg imatinib daily	Subjects in this arm received 350 mg of BYL719 in combination with 400 mg imatinib daily	All patients enrolled in the study.
Total participants affected	1 (25.00%)	1 (16.67%)	10 (21.74%)	12 (21.43%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events (AEs) were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 54.4 months.
Additional Description	AE description; Any sign or symptom that occurs during the study treatment plus the 30 days post treatment
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment

	BYL 200mg + STI 400mg N = 4	**BYL 250mg + STI 400mg N = 6**	**BYL 350mg + STI 400mg N = 46**	**All@patients N = 56**
Arm/Group Description	Subjects in this arm received 200 mg of BYL719 in combination with 400 mg imatinib daily	Subjects in this arm received 250 mg of BYL719 in combination with 400 mg imatinib daily	Subjects in this arm received 350 mg of BYL719 in combination with 400 mg imatinib daily	All patients enrolled in the study.
Total participants affected	1 (25.00%)	4 (66.67%)	25 (54.35%)	30 (53.57%)
Blood and lymphatic system disorders				
Anaemia	0 (0.00%)	1 (16.67%)	2 (4.35%)	3 (5.36%)
Cardiac disorders				
Atrial fibrillation	0 (0.00%)	0 (0.00%)	2 (4.35%)	2 (3.57%)
Cardiac failure	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Gastrointestinal disorders				
Abdominal pain	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Ascites	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)

Constipation	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Diarrhoea	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Gastric perforation	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Gastrointestinal haemorrhage	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Intestinal haemorrhage	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Intestinal obstruction	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Intestinal perforation	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Nausea	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Pancreatitis	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Peritoneal haemorrhage	0 (0.00%)	0 (0.00%)	2 (4.35%)	2 (3.57%)
Upper gastrointestinal haemorrhage	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Vomiting	0 (0.00%)	0 (0.00%)	2 (4.35%)	2 (3.57%)
General disorders and administration site conditions				
Asthenia	0 (0.00%)	0 (0.00%)	2 (4.35%)	2 (3.57%)
Fatigue	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
General physical health deterioration	0 (0.00%)	0 (0.00%)	2 (4.35%)	2 (3.57%)
Generalised oedema	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Malaise	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Multiple organ dysfunction syndrome	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Pyrexia	0 (0.00%)	2 (33.33%)	1 (2.17%)	3 (5.36%)
Hepatobiliary disorders				
Cholangitis	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)

Immune system disorders				
Drug hypersensitivity	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Infections and infestations				
Abdominal abscess	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Lung infection	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Rectal abscess	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Sepsis	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Subcutaneous abscess	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Urinary tract infection	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Investigations				
Aspartate aminotransferase increased	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Blood bilirubin increased	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Blood creatinine increased	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Electrocardiogram abnormal	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Platelet count decreased	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Transaminases increased	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
White blood cell count increased	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Metabolism and nutrition disorders				
Decreased appetite	1 (25.00%)	0 (0.00%)	2 (4.35%)	3 (5.36%)
Dehydration	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Fluid retention	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)

Hyperglycaemia	0 (0.00%)	0 (0.00%)	2 (4.35%)	2 (3.57%)
Hyperuricaemia	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Hypoalbuminaemia	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Nervous system disorders				
Encephalopathy	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Psychiatric disorders				
Completed suicide	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Renal and urinary disorders				
Acute kidney injury	0 (0.00%)	0 (0.00%)	2 (4.35%)	2 (3.57%)
Proteinuria	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Renal impairment	1 (25.00%)	0 (0.00%)	2 (4.35%)	3 (5.36%)
Ureteric obstruction	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Pleural effusion	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Respiratory failure	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)
Skin and subcutaneous tissue disorders				
Rash	0 (0.00%)	0 (0.00%)	1 (2.17%)	1 (1.79%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events (AEs) were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 54.4 months.
Additional Description	AE description; Any sign or symptom that occurs during the study treatment plus the 30 days post treatment
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	BYL 200mg + STI 400mg N = 4	**BYL 250mg + STI 400mg N = 6**	**BYL 350mg + STI 400mg N = 46**	**All@patients N = 56**
Arm/Group Description	Subjects in this arm received 200 mg of BYL719 in combination with 400 mg imatinib daily	Subjects in this arm received 250 mg of BYL719 in combination with 400 mg imatinib daily	Subjects in this arm received 350 mg of BYL719 in combination with 400 mg imatinib daily	All patients enrolled in the study.
Total participants affected	4 (100.00%)	6 (100.00%)	46 (100.00%)	56 (100.00%)
Blood and lymphatic system disorders				
Anaemia	2 (50.00%)	3 (50.00%)	9 (19.57%)	14 (25.00%)
Leukopenia	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Eye disorders				
Eye pruritus	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Eyelid oedema	0 (0.00%)	0 (0.00%)	5 (10.87%)	5 (8.93%)
Periorbital oedema	1 (25.00%)	1 (16.67%)	3 (6.52%)	5 (8.93%)
Gastrointestinal disorders				
Abdominal discomfort	0 (0.00%)	0 (0.00%)	3 (6.52%)	3 (5.36%)

Abdominal distension	0 (0.00%)	1 (16.67%)	1 (2.17%)	2 (3.57%)
Abdominal pain	0 (0.00%)	3 (50.00%)	12 (26.09%)	15 (26.79%)
Abdominal pain upper	1 (25.00%)	4 (66.67%)	4 (8.70%)	9 (16.07%)
Anal fissure	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Anal sphincter hypertonia	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Ascites	0 (0.00%)	0 (0.00%)	3 (6.52%)	3 (5.36%)
Constipation	2 (50.00%)	2 (33.33%)	6 (13.04%)	10 (17.86%)
Diarrhoea	3 (75.00%)	3 (50.00%)	23 (50.00%)	29 (51.79%)
Dry mouth	0 (0.00%)	0 (0.00%)	5 (10.87%)	5 (8.93%)
Dyspepsia	0 (0.00%)	0 (0.00%)	7 (15.22%)	7 (12.50%)
Epigastric discomfort	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Gastrooesophageal reflux disease	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Nausea	3 (75.00%)	3 (50.00%)	30 (65.22%)	36 (64.29%)
Oesophagitis	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Rectal haemorrhage	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Stomatitis	1 (25.00%)	1 (16.67%)	3 (6.52%)	5 (8.93%)
Vomiting	1 (25.00%)	1 (16.67%)	18 (39.13%)	20 (35.71%)
General disorders and administration site conditions				
Asthenia	3 (75.00%)	2 (33.33%)	9 (19.57%)	14 (25.00%)
Chills	0 (0.00%)	1 (16.67%)	2 (4.35%)	3 (5.36%)
Early satiety	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Fatigue	0 (0.00%)	1 (16.67%)	14 (30.43%)	15 (26.79%)
Influenza like illness	0 (0.00%)	1 (16.67%)	2 (4.35%)	3 (5.36%)
Oedema peripheral	0 (0.00%)	0 (0.00%)	14 (30.43%)	14 (25.00%)

Pyrexia	1 (25.00%)	3 (50.00%)	4 (8.70%)	8 (14.29%)
Hepatobiliary disorders				
Cholestasis	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Hepatic pain	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Hyperbilirubinaemia	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Infections and infestations				
Cystitis	1 (25.00%)	0 (0.00%)	1 (2.17%)	2 (3.57%)
Gingivitis	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Nasopharyngitis	1 (25.00%)	0 (0.00%)	3 (6.52%)	4 (7.14%)
Oral herpes	1 (25.00%)	0 (0.00%)	1 (2.17%)	2 (3.57%)
Respiratory tract infection	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Rhinitis	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Investigations				
Alanine aminotransferase increased	2 (50.00%)	2 (33.33%)	3 (6.52%)	7 (12.50%)
Amylase increased	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Aspartate aminotransferase increased	2 (50.00%)	2 (33.33%)	4 (8.70%)	8 (14.29%)
Blood alkaline phosphatase increased	3 (75.00%)	2 (33.33%)	3 (6.52%)	8 (14.29%)
Blood bilirubin increased	2 (50.00%)	0 (0.00%)	2 (4.35%)	4 (7.14%)
Blood cholesterol increased	2 (50.00%)	0 (0.00%)	2 (4.35%)	4 (7.14%)
Blood creatine phosphokinase increased	0 (0.00%)	1 (16.67%)	1 (2.17%)	2 (3.57%)

Blood creatinine increased	3 (75.00%)	1 (16.67%)	6 (13.04%)	10 (17.86%)
Blood lactate dehydrogenase increased	2 (50.00%)	0 (0.00%)	2 (4.35%)	4 (7.14%)
Blood urea increased	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Blood uric acid increased	2 (50.00%)	0 (0.00%)	1 (2.17%)	3 (5.36%)
Gamma-glutamyltransferase increased	1 (25.00%)	3 (50.00%)	4 (8.70%)	8 (14.29%)
Insulin C-peptide increased	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Lipase decreased	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Lipase increased	1 (25.00%)	1 (16.67%)	2 (4.35%)	4 (7.14%)
Protein urine	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Troponin T increased	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Weight decreased	0 (0.00%)	1 (16.67%)	7 (15.22%)	8 (14.29%)
Metabolism and nutrition disorders				
Decreased appetite	2 (50.00%)	2 (33.33%)	17 (36.96%)	21 (37.50%)
Hyperalbuminaemia	1 (25.00%)	0 (0.00%)	1 (2.17%)	2 (3.57%)
Hypercalcaemia	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Hyperglycaemia	1 (25.00%)	1 (16.67%)	30 (65.22%)	32 (57.14%)
Hyperlipasaemia	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Hypertriglyceridaemia	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Hyperuricaemia	1 (25.00%)	0 (0.00%)	1 (2.17%)	2 (3.57%)
Hypoalbuminaemia	1 (25.00%)	1 (16.67%)	3 (6.52%)	5 (8.93%)
Hypocalcaemia	0 (0.00%)	1 (16.67%)	4 (8.70%)	5 (8.93%)

Hypokalaemia	0 (0.00%)	1 (16.67%)	7 (15.22%)	8 (14.29%)
Hypomagnesaemia	2 (50.00%)	0 (0.00%)	1 (2.17%)	3 (5.36%)
Hyponatraemia	0 (0.00%)	1 (16.67%)	3 (6.52%)	4 (7.14%)
Musculoskeletal and connective tissue disorders				
Back pain	1 (25.00%)	0 (0.00%)	2 (4.35%)	3 (5.36%)
Muscle spasms	0 (0.00%)	3 (50.00%)	8 (17.39%)	11 (19.64%)
Musculoskeletal pain	0 (0.00%)	1 (16.67%)	3 (6.52%)	4 (7.14%)
Myalgia	0 (0.00%)	1 (16.67%)	3 (6.52%)	4 (7.14%)
Pain in extremity	2 (50.00%)	0 (0.00%)	1 (2.17%)	3 (5.36%)
Spinal pain	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Tumour haemorrhage	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Nervous system disorders				
Dysgeusia	0 (0.00%)	0 (0.00%)	9 (19.57%)	9 (16.07%)
Headache	2 (50.00%)	0 (0.00%)	6 (13.04%)	8 (14.29%)
Sciatica	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Psychiatric disorders				
Depression	1 (25.00%)	0 (0.00%)	2 (4.35%)	3 (5.36%)
Insomnia	2 (50.00%)	1 (16.67%)	4 (8.70%)	7 (12.50%)
Sleep disorder	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Renal and urinary disorders				
Proteinuria	1 (25.00%)	0 (0.00%)	2 (4.35%)	3 (5.36%)

Renal colic	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Reproductive system and breast disorders				
Erectile dysfunction	0 (0.00%)	1 (16.67%)	1 (2.17%)	2 (3.57%)
Oedema genital	0 (0.00%)	0 (0.00%)	3 (6.52%)	3 (5.36%)
Respiratory, thoracic and mediastinal disorders				
Cough	2 (50.00%)	0 (0.00%)	3 (6.52%)	5 (8.93%)
Hiccups	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Nasal pruritus	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Oropharyngeal pain	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (1.79%)
Rhinorrhoea	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (1.79%)
Skin and subcutaneous tissue disorders				
Alopecia	0 (0.00%)	0 (0.00%)	3 (6.52%)	3 (5.36%)
Dry skin	0 (0.00%)	0 (0.00%)	5 (10.87%)	5 (8.93%)
Pruritus	0 (0.00%)	0 (0.00%)	5 (10.87%)	5 (8.93%)
Rash	0 (0.00%)	0 (0.00%)	10 (21.74%)	10 (17.86%)
Rash maculo-papular	0 (0.00%)	0 (0.00%)	7 (15.22%)	7 (12.50%)
Vascular disorders				
Hypertension	0 (0.00%)	0 (0.00%)	4 (8.70%)	4 (7.14%)

Other Relevant Findings

Not Applicable

Conclusion:

The study met its primary objective and alpelisib 350 mg once daily was declared as MTD in combination with imatinib 400 mg once daily when administered orally in subjects with metastatic and/or unresectable GIST.

The safety and tolerability profile of alpelisib plus imatinib combination observed in the current study was consistent with prior experience of alpelisib and imatinib as single agents in an advanced oncology setting.

The efficacy results from this study suggested that the combination of alpelisib and imatinib failed to corroborate the expected strong synergistic activity on tumor cell inhibition of the PDGFRα and/PI3K signaling pathways.

Date of Clinical Trial Report

28 May 2019