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Generic Drug Name

Sonidegib

Trial Indication(s)

Advanced solid tumors

Protocol Number

CLDE225A2112

Protocol Title

A Phase Ib, multi-center, two parallel group, open-label, drug-drug interaction study to assess the effect of LDE225 on the pharmacokinetics of bupropion and warfarin in patients with advanced solid tumors

Clinical Trial Phase

Phase Ib

Phase of Drug Development

Phase III

Study Start/End Dates

Study initiation date: 29-Apr-2013 (first patient first visit)

Study completion date: 03-Aug-2016 (last patient last visit)

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Reason for Termination (If applicable): NA

Study Design/Methodology

This was a multi-center, parallel group design, open-label study to evaluate the impact of sonidegib on the pharmacokinetics (PK) of warfarin and bupropion in patients with advanced solid tumors. Patients were divided into two groups. For both groups there was a probe drug PK-run in period, followed by sonidegib QD treatment. Group 1 patients received warfarin 15 mg single dose tablet on Day 1 of probe drug run-in period and Cycle 2 Day 22 (C2D22) of sonidegib administration. Group 2 patients received bupropion 75 mg tablet on Day 1 of probe drug run-in period and during C2D22 of sonidegib administration. For both groups, LDE225 800 mg once daily dosing began on Cycle 1 day 1 of a 28-day cycle. Treatment with sonidegib for both groups continued until the patient experienced unacceptable toxicity, disease progression, withdrawal of consent and/or at the discretion of the Investigator.

Centers

This study was conducted at 13 centers in the United States

Publication:

N/A

Objectives:

Primary objective

To evaluate the effect of sonidegib on the PK profile of warfarin and bupropion in patients with advanced solid tumors.

Key secondary objective

To evaluate the effects of sonidegib on the pharmaco dynamic (PD) activity of warfarin in patients with advanced solid tumors

To evaluate the safety and tolerability of sonidegib when administered alone and concomitantly with either bupropion or warfarin, in patients with advanced solid tumors.

Other secondary objectives

To evaluate the preliminary evidence of anti-tumor activity of sonidegib in patients with advanced solid tumors

To further assess the effect of sonidegib treatment on cardiac function.

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

The investigation drugs used in this study were Sonidegib, warfarin and bupropion.

Sonidegib was administered at a dose of 800 mg (200 x 4 mg) QD beginning on C1D1 of a 28-day cycle.

Warfarin 15 mg single dose (oral tablet) on study start (Day 1 and on C2D22 of sonidegib treatment).

Bupropion 75 mg single dose (oral tablet) on study start (Day 1 and on C2D22 of sonidegib treatment).

Statistical Methods

A formal statistical analysis was performed for the primary variables (AUClast, AUCinf, and Cmax) separately for S-warfarin, R-warfarin, and bupropion at PK run-in and C2D22 using the respective PAS. A linear mixed model was fitted to the log-transformed PK parameters to assess the effect of sonidegib on S-warfarin and R-warfarin (Group 1), and sonidegib on bupropion (Group 2).

For each primary PK parameter (AUClast, AUCinf, or Cmax) of S-warfarin, R-warfarin, and bupropion, individual patient ratios and geometric mean ratio of test vs. reference with 90% CI were plotted by treatment using the respective PAS.

Descriptive statistics (n, geometric mean and CV%, mean and CV %, median, SD, minimum, and maximum) were presented for all PK parameters for S-warfarin, R-warfarin, 7-hydroxy-S-warfarin, bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion by treatment (warfarin and sonidegib+warfarin for Group 1; bupropion and sonidegib+bupropion for Group 2) using the respective PAS. Since Tmax was generally evaluated using distribution-free methods, only median values and ranges were given for this parameter.

A listing of PK parameters for S-warfarin, R-warfarin, 7-hydroxy-S-warfarin, bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion was generated separately using FAS.

Summary statistics for S-warfarin, R-warfarin, 7-hydroxy-S-warfarin, bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion concentrations were presented at each scheduled time point using the respective PAS, as well as for sonidegib concentrations using Safety set.

Figures of geometric mean together with arithmetic mean (SD) concentration-time profiles on linear-linear and log-linear scale by treatment were provided for S-warfarin, R-warfarin, and 7-hydroxy-S-warfarin (Group 1, 0-144 hours) and bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion (Group 2, 0-96 hours) using the respective PAS.

Individual concentration-time profiles with median were plotted for both warfarin (0 144 hours) and bupropion (0-96 hours) metabolites using FAS.

Geometric mean and arithmetic mean (SD) trough concentration-time profiles were plotted for sonidegib using Safety set.

Listings of warfarin and bupropion concentrations were generated using FAS. A listing of sonidegib concentrations was generated using FAS.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

1. Written informed consent obtained prior to any screening procedures

2. Patients with cytopathologically or histopathologically confirmed diagnosis of an advanced solid tumor which had progressed despite standard therapy, or for which no standard therapy exists or patients with locally advanced or metastatic basal cell carcinoma who were not amenable or eligible for standard therapy.

3. Aged ≥ 18 years

4. WHO performance status ≤ 2

5. All of the following laboratory parameters

   - Absolute neutrophil count (ANC) ≥ 1.5 x 109/L
   - Platelets ≥ 100 x 109/L
   - Hemoglobin ≥ 9 g/dL
   - Serum creatinine ≤ 1.5 x upper limit of normal range (ULN)
   - Serum creatine phosphokinase (CK) level ≤ 1.5 x ULN

•Bilirubin ≤ 1.5 x ULN

•Aspartate amino transferase (AST; serum glutamate oxaloacetate transferase; SGOT) and alanine amino transferase (ALT; serum glutamate pyruvate trasferase; SGPT) ≤ 2.5 x ULN if liver metastases were not present or ≤ 5 x ULN if liver metastases were present.

Exclusion Criteria

1. Central nervous system (CNS) tumors were excluded, when a patients with a history of brain metastases or as assessed by radiologic imaging (e.g. computed tomography (CT) or magnetic resonance imaging (MRI) scan).

2. Systemic anticancer treatment (including biologic therapy/antibodies) within 2 weeks before first dose of study treatment (6 weeks for nitrosourea, mitomycin, and monoclonal antibodies).

3. Radiation therapy within 4 weeks before first dose of probe drug.

4. Investigational agents within 4 weeks or ≤ 10 x T1/2 (whichever was longer) before start of study treatment.

5. Unresolved toxicity greater than common terminology criteria for adverse events (CTCAE) grade 1 from previous anticancer therapy or radiation therapy (excluding neurotoxicity, alopecia, ototoxicity, lymphopenia (inclusion of a patient with ongoing lymphopenia > CTCAE grade 1 from prior therapy) or other specifications in the eligibility criteria for this study), or incomplete recovery from previous surgery.

6. Patients with known allergy/hypersensitivity to warfarin or bupropion and/or related compounds (applied to relevant probe group only)

7. Patients with a history of/or active bleeding disorders (only applied to warfarin group)

8. Patients receiving treatment with vitamin K, Coumadin or other agents containing warfarin and heparin. Heparin flush to maintain patency of a central venous access device was allowed (only applies to warfarin group; patients in bupropion group could receive non-coumadin based anticoagulation therapy).

9. Patients receiving treatment with bupropion.

10. Patients receiving treatment with medications that are known to be strong inhibitors or inducers of CYP3A4/5 (including St John's wort) within 4 weeks prior to first dose of study treatment.

11. Patients who were receiving treatment with medications that are metabolized by CYP2B6 and CYP2C9, that have narrow therapeutic indices that could not be discontinued at least 1 week before start of study treatment, and for the duration of the study

12. Administration of CYP2C9 enzyme inducing or inhibition drugs (e.g. fluconazole, fluvastatin) within 4 weeks prior to first dose of study treatment (only applies to warfarin group).

13. Administration of CYP2B6 enzyme inducing or inhibition drugs (e.g. phenobarbital, phenytoin, thiotepa, ticlopidine, orphenadrine, clopidogrel) within 4 weeks prior to first dose of study treatment (only applies to bupropion group).

14. Patients who were on concomitant treatment with drugs that are recognized to cause rhabdomyolysis, such as HMG CoA (3-hydroxy-3-methyl-glutaryl-CoA reductase) inhibitors (statins), clofibrate and gemfibrozil, and that could not be discontinued at least 2 weeks prior to starting sonidegib treatment. If it was essential that the patient stayed on a statin to control hyperlipidemia only pravastatin could be used with extra caution

15. Patients who were receiving systemic corticosteroids

16. Patients with bipolar disorder or history of seizure, cranial trauma, or other predispositions toward seizure (only applies to bupropion group)

17. Major surgery, serious illness, or traumatic injury within 2 weeks of starting study therapy. Insertion of a central venous access device was not considered major surgery

18. Patients anticipated to require major surgery within the first 2 cycles of treatment

19. Patients who required a nasogastric tube for drug administration

20. Any concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes, uncontrolled diarrhea, autoimmune disease including lupus, psoriasis, inflammatory bowel disease, severe infection, severe hypertension or severe cardiovascular disease or clinically significant ECG abnormalities) that in the investigator’s opinion could put the patient at greater risk for treatment-related toxicities or confound the interpretation of clinical outcomes

21. Patients who had neuromuscular disorders that were associated with elevated creatinine kinase (CK) (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

22. Impaired cardiac function or clinically significant heart disease, including any one of the following:

- Clinically significant heart disease (e.g., congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
- Corrected QT (QTc) interval corrected for heart rate using Fridericia's formula [QTcF] > 450 msec for males and > 470 msec for females on the screening ECG
- A past medical history of clinically significant ECG abnormalities or a family history of prolonged QT-interval syndrome
- Angina pectoris within 3 months of study entry
- Acute myocardial infarction within 3 months of study entry

23. Pregnant or nursing (lactating) women, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (> 5 mIU/mL)

24. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are using two forms of highly effective contraception, as shown below, throughout the study and for 20 months after the last treatment.

25. Known diagnosis of human immunodeficiency virus (HIV), hepatitis B or C (testing was not mandatory for study entry)

26. Impairment of gastrointestinal function or gastrointestinal disease (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection)

27. Patients who in the Investigators' opinion could be unwilling, unable or unlikely to comply with the requirements of the study protocol.

28. Patients who were planning on embarking on a new strenuous exercise regimen after initiation of study treatment. Note: Muscular activities, such as strenuous exercise, that could result in significant increases in CK levels had to be avoided whilst on sonidegib treatment.

29. Patients who had previously been treated with systemic sonidegib or with other Hedgehog (Hh) pathway inhibitors.

30. Smokers (use of tobacco products or products containing nicotine within 1 month prior to dosing). Smokers were defined as any patient who reports cigarette use during the preceding 30 days prior to probe drug dosing or has a urine cotinine > 500 ng/mL. Smoking or the use of nicotine-containing produces was not permitted during the course of the study.

31. Patients with known ongoing alcohol and/or drug abuse within 1 month prior to probe drug dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening/baseline evaluations.

32. Patients who were not willing to follow the specified alcohol restrictions. Patients had to abstain from alcohol 48 hours prior to probe drug dosing on the day of probe drug dosing and during the DDI assessment periods. On other days, a limit of 1 drink per day through the first 2 cycles (8 weeks) of the study.

Participant Flow Table

Patient disposition-Group 1 (FAS)

Disposition Reason	All patients (N=61) n (%)
Patient treated	
End of treatment	61 (100.0)
Primary reason for end of treatment	
disease progression	44 (72.1)
adverse event(s)	14 (23.0)
subject withdrew consent	3 (4.9)
Primary reason for study evaluation completion	
f/u phase complication as per protocol	29 (47.5)
death	14 (23.0)
subject withdrew consent	6 (9.8)
disease progression	3 (4.9)
protocol deviation	3 (4.9)
administrative problems	1 (1.6)

Patient disposition-Group 2 (FAS)

Disposition Reason	All patients (N=51) n (%)

Disposition Reason	All patients (N=51) n (%)
Patient treated	
End of treatment	51 (100.0)
Primary reason for end of treatment	
disease progression	41 (80.4)
adverse event(s	4 (7.8)
subject withdrew consent	2 (3.9)
death	2 (3.9)
administrative problems	1 (2.0)
protocol deviation	1 (2.0)
Primary reason for study evaluation completion	
F/u phase completion as per protocol	32 (62.7)
death	11 (21.6)
subject withdrew consent	2 (3.9)
Lost to follow-up	1 (2.0)
Disease progression	1 (2.0)
Protocol deviation	1 (2.0)

Baseline Characteristics

Demographic Group 1 (FAS)

Demographic variable	All patients (N=61)
Age (years)	
n	61
Mean	60.7

Demographic variable	All patients (N=61)
SD	12.14
Median	63.0
Minimum	27
Maximum	78
Age category (years)-n (%)	
<65	33 (54.1)
≥65	28 (45.9)
Sex - n (%)	
Female	34 (55.7)
Male	27 (44.3)
Race - n (%)	
Caucasian	56 (91.8)
Black	4 (6.6)
Other	1 (1.6)
Ethnicity - n (%)	
Other	46 (75.4)
Hispanic/Latino	13 (21.3)
Mixed Ethnicity	1 (1.6)
Missing	1 (1.6)
Body mass index (kg/m^2)	
n	58
Mean	28.217
SD	8.1078
Median	26.425
Minimum	17.07
Maximum	65.18
ECOG performance status-n (%)	
0	15 (24.6)

Demographic variable	All patients (N=61)
1	45 (73.8)
2	1 (1.6)

Baseline weight (kg) and baseline height (cm) were defined as the last non-missing assessment of weight and height before study treatment.
BMI (kg/m^2) = weight (kg) / height $(m)^2$.
BMI and BSA are calculated using the baseline weight and baseline height.

Demographic Group 2 (FAS)

Demographic variable	All patients (N=51)
Age (years)	
n	51
Mean	60.7
SD	14.01
Median	63.0
Minimum	22
Maximum	83
Age category (years)-n (%)	
<65	27 (52.9)
≥65	24 (41.2)
Sex - n (%)	
Female	21 (41.2)
Male	30 (58.8)
Race - n (%)	
Caucasian	46 (90.2)
Black	3 (5.9)
Other	2 (3.9)
Ethnicity - n (%)	
Other	44 (86.3)

Demographic variable	All patients (N=51)
Hispanic/Latino	7 (13.7)
Body mass index (kg/m^2)	
n	50
Mean	27.662
SD	6.7988
Median	27.245
Minimum	14.04
Maximum	47.22
ECOG performance status-n (%)	
0	13 (25.5)
1	34 (66.7)
2	4 (7.8)

Baseline weight (kg) and baseline height (cm) were defined as the last non-missing assessment of weight and height before study treatment.
BMI (kg/m^2) = weight (kg) / height (m)^2.
BMI and BSA are calculated using the baseline weight and baseline height.

Primary Outcome Result(s)

Summary of primary PK parameters for S-warfarin by treatment – Group 1 (PAS)

Treatment	Statistics	AUCinf (ng*hr/mL)	AUClast (ng*hr/mL)	Cmax (ng/mL)
WARFARIN (N=19)	n	18	19	19
	Mean	29000	28400	896
	SD	9760	12100	235
	CV% mean	33.7	42.7	26.3
	Geo-mean	27200	26200	868
	CV% geo-mean	39.8	44.0	26.2
	Median	29500	28700	918

Treatment	Statistics	AUCinf (ng*hr/mL)	AUClast (ng*hr/mL)	Cmax (ng/mL)
	[Min; Max]	[10400; 49600]	[9320; 66100]	[510; 1550]
LDE225+WARFARIN (N=19)	n	16	19	19
	Mean	32200	33200	817
	SD	12300	17400	300
	CV% mean	38.2	52.5	36.7
	Geo-mean	29900	29900	766
	CV% geo-mean	42.4	48.1	39.0
	Median	31500	30500	767
	[Min; Max]	[12700; 61400]	[11600; 92600]	[328; 1580]

n = number of patients with non-missing values.
CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Summary of statistical analysis of primary PK parameters for S-warfarin – Group 1 (PAS)

					Treatment comparison		
						90% C	
PK parameter (unit)	Treatment	n*	Adjusted geo-mean	Comparison(s)	Geo-mean ratio	Lower	Upper
AUCinf (ng*hr/mL)	WARFARIN	18	27200				
	LDE225+WARFARIN	16	31400	LDE225+WARFARIN/WARFARIN	1.15	1.07	1.24
AUClast (ng*hr/mL)	WARFARIN	19	26200				
	LDE225+WARFARIN	19	29900	LDE225+WARFARIN/WARFARIN	1.14	1.07	1.22
Cmax (ng/mL)	WARFARIN	19	868				
	LDE225+WARFARIN	19	766	LDE225+WARFARIN/WARFARIN	0.882	0.805	0.967

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Summary of primary PK parameters for R-warfarin by treatment – Group 1 (PAS)

Treatment	Statistics	AUCinf (ng*hr/mL)	AUClast (ng*hr/mL)	Cmax (ng/mL)
WARFARIN (N=19)	n	7	19	19
	Mean	51000	45200	863
	SD	15200	11000	227
	CV% mean	29.9	24.3	26.3
	Geo-mean	48800	43700	836
	CV% geo-mean	34.4	28.5	26.3
	Median	48800	46200	873
	[Min; Max]	[25900; 74000]	[22800; 63000]	[473; 1500]
LDE225+WARFARIN (N=19)	n	10	19	19
	Mean	54500	48900	816
	SD	10500	11400	259
	CV% mean	19.2	23.3	31.7
	Geo-mean	53400	47500	776
	CV% geo-mean	22.0	26.2	34.3
	Median	57000	50200	828
	[Min; Max]	[32000; 66900]	[27000; 67200]	[398; 1440]

Summary of statistical analysis of primary PK parameters for R-warfarin – Group 1 (PAS)

					Treatment comparison		
						90% CI	
PK parameter (unit)	Treatment	n*	Adjusted geo-mean	Comparison(s)	Geo-mean ratio	Lower	Upper
AUCinf (ng*hr/mL)	WARFARIN	7	48400				
	LDE225+WARFARIN	10	53400	LDE225+WARFARIN/WARFARIN	1.10	0.979	1.24

PK parameter (unit)	Treatment	n*	Adjusted geo-mean	Comparison(s)	Treatment comparison Geo-mean ratio	90% CI Lower	90% CI Upper
AUClast (ng*hr/mL)	WARFARIN	19	43700				
	LDE225+WARFARIN	19	47500	LDE225+WARFARIN/WARFARIN	1.09	1.03	1.15
Cmax (ng/mL)	WARFARIN	19	836				
	LDE225+WARFARIN	19	776	LDE225+WARFARIN/WARFARIN	0.928	0.866	0.995

Summary of statistical analysis of PD parameters for warfarin – Group 1 (PDAS)

PD parameter (unit)	Treatment	n*	Adjusted Geo-mean	Comparison(s)	Treatment comparison Geo-mean Ratio	90% CI Lower	90% CI Upper
PTmax (sec)	WARFARIN	17	2100				
	LDE225+ WARFARIN	17	2190	LDE225+WARFARIN/WARFARIN	1.04	0.984	1.10
PTauc (sec*hr)	WARFARIN	17	18.2				
	LDE225+ WARFARIN	17	19.6	LDE225+WARFARIN/WARFARIN	1.08	1.00	1.15
INRmax	WARFARIN	17	197				
	LDE225+ WARFARIN	17	205	LDE225+WARFARIN/WARFARIN	1.04	0.985	1.09
INRauc (hr)	WARFARIN	17	1.69				

PD parameter (unit)	Treatment	n*	Adjusted Geo-mean	Comparison(s)	Treatment comparison Geo-mean Ratio	90% CI Lower	90% CI Upper
	LDE225+ WARFARIN	17	1.82	LDE225+WARFARIN/WARFARIN	1.08	1.01	1.15

Summary of PD parameters for warfarin by treatment – Group 1 (PDAS)

Treatment	Statistics	PTauc (sec*hr)	PTmax (sec)	INRauc (hr)	INRmax
WARFARIN (N=19)	n	17	17	17	17
	Mean (SD)	2150 (518)	18.9 (5.90)	201 (45.4)	1.75 (0.513)
	CV% mean	24.1	31.2	22.6	29.4
	Geo-mean	2100	18.2	197	1.69
	CV% geo-mean	20.2	27.7	19.2	26.2
	Median	1950	17.3	183	1.61
	[Min; Max]	[1770; 3810]	[13.3; 35.2]	[167; 346]	[1.25; 3.16]
LDE225+WARFARIN (N=19)	n	17	17	17	17
	Mean (SD)	2260 (686)	20.4 (6.47)	211 (60.1)	1.88 (0.565)
	CV% mean	30.4	31.7	28.5	30.0
	Geo-mean	2190	19.6	205	1.82
	CV% geo-mean	24.9	29.0	23.7	27.6
	Median	1970	17.7	189	1.64
	[Min; Max]	[1690; 4580]	[14.8; 37.6]	[159; 412]	[1.39; 3.36]

Summary of primary PK parameters for bupropion by treatment – Group 2 (PAS)

Treatment	Statistics	AUCinf (ng*hr/mL)	AUClast (ng*hr/mL)	Cmax (ng/mL)
BUPROPION (N=14)	n	14	14	14
	Mean	618	580	107

Treatment	Statistics	AUCinf (ng*hr/mL)	AUClast (ng*hr/mL)	Cmax (ng/mL)
	SD	253	251	65.9
	CV% mean	40.9	43.3	61.4
	Geo-mean	578	538	93.3
	CV% geo-mean	38.3	40.6	56.4
	Median	548	503	87.1
	[Min; Max]	[342; 1270]	[297; 1240]	[44.3; 293]
LDE225+BUPROPION (N=14)	n	14	14	14
	Mean	696	656	127
	SD	335	329	71.9
	CV% mean	48.2	50.2	56.7
	Geo-mean	635	594	109
	CV% geo-mean	44.6	46.7	64.3
	Median	604	569	107
	[Min; Max]	[399; 1330]	[370; 1300]	[45.2; 267]

Summary of statistical analysis of primary PK parameters for bupropion – Group 2 (PAS)

					Treatment comparison		
						90% CI	
PK parameter (unit)	Treatment	n*	Adjusted geo-mean	Comparison(s)	Geo-mean ratio	Lower	Upper
AUCinf (ng*hr/mL)	BUPROPION	14	578				
	LDE225+BUPROPION	14	635	LDE225+BUPROPION/BUPROPION	1.10	0.987	1.23
AUClast (ng*hr/mL)	BUPROPION	14	538				
	LDE225+BUPROPION	14	594	LDE225+BUPROPION/BUPROPION	1.10	0.992	1.23

PK parameter (unit)	Treatment	n*	Adjusted geo-mean	Comparison(s)	Treatment comparison Geo-mean ratio	90% CI Lower	90% CI Upper
Cmax (ng/mL)	BUPROPION	14	93.3				
	LDE225+BUPROPION	14	109	LDE225+BUPROPION/BUPROPION	1.16	0.952	1.42

Summary of Safety

Safety Results

Adverse events with at least 5% incidence, regardless of study drug relationship, by primary system organ class and maximum grade – Group 1 (Safety set)

Primary system organ class	All patients N=61 All grades n (%)	All patients N=61 Grade 3/4 n (%)
Any primary system organ class	61 (100.0)	38 (62.3)
Blood and lymphatic system disorders	11 (18.0)	5 (8.2)
Cardiac disorders	6 (9.8)	1 (1.6)
Gastrointestinal disorders	47 (77.0)	8 (13.1)
General disorders and administration site conditions	36 (59.0)	4 (6.6)
Infections and infestations	18 (29.5)	5 (8.2)
Injury, poisoning and procedural complications	5 (8.2)	1 (1.6)
Investigations	40 (65.6)	17 (27.9)
Metabolism and nutrition disorders	30 (49.2)	11 (18.0)
Musculoskeletal and connective tissue disorders	40 (65.6)	5 (8.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (8.2)	4 (6.6)
Nervous system disorders	26 (42.6)	2 (3.3)

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Primary system organ class	All patients N=61	
	All grades n (%)	Grade 3/4 n (%)
Psychiatric disorders	10 (16.4)	1 (1.6)
Renal and urinary disorders	13 (21.3)	5 (8.2)
Respiratory, thoracic and mediastinal disorders	25 (41.0)	4 (6.6)
Skin and subcutaneous tissue disorders	12 (19.7)	0
Vascular disorders	6 (9.8)	0

Primary system organ classes are presented alphabetically.
A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Adverse events with at least 5% incidence, regardless of study drug relationship, by primary system organ class and maximum grade – Group 2 (Safety set)

Primary system organ class	All patients N=51	
	All grades n (%)	Grade 3/4 n (%)
Any primary system organ class	50 (98.0)	28 (54.9)
Blood and lymphatic system disorders	14 (27.5)	7 (13.7)
Cardiac disorders	7 (13.7)	1 (2.0)
Gastrointestinal disorders	35 (68.6)	7 (13.7)
General disorders and administration site conditions	31 (60.8)	4 (7.8)
Infections and infestations	9 (17.6)	3 (5.9)
Injury, poisoning and procedural complications	5 (9.8)	0
Investigations	22 (43.1)	11 (21.6)
Metabolism and nutrition disorders	27 (52.9)	9 (17.6)
Musculoskeletal and connective tissue disorders	31 (60.8)	5 (9.8)
Nervous system disorders	25 (49.0)	4 (7.8)

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Primary system organ class	All patients N=51	
	All grades n (%)	Grade 3/4 n (%)
Psychiatric disorders	12 (23.5)	0
Renal and urinary disorders	12 (23.5)	3 (5.9)
Reproductive system and breast disorders	3 (5.9)	0
Respiratory, thoracic and mediastinal disorders	18 (35.3)	5 (9.8)
Skin and subcutaneous tissue disorders	8 (15.7)	1 (2.0)
Vascular disorders	9 (17.6)	0

Primary system organ classes are presented alphabetically.
A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Adverse events with at least 5% incidence, regardless of study drug relationship, by preferred term and maximum grade – Group 1 (Safety set)

Preferred term	All patients N=61	
	All grades n (%)	Grade 3/4 n (%)
Total	61 (100.0)	38 (62.3)
Fatigue	23 (37.7)	1 (1.6)
Nausea	21 (34.4)	2 (3.3)
Decreased appetite	17 (27.9)	3 (4.9)
Vomiting	17 (27.9)	3 (4.9)
Constipation	16 (26.2)	1 (1.6)
Abdominal pain	14 (23.0)	3 (4.9)
Myalgia	13 (21.3)	0
Back pain	12 (19.7)	1 (1.6)

Preferred term	All patients N=61	
	All grades n (%)	Grade 3/4 n (%)
Blood creatine phosphokinase increased	11 (18.0)	7 (11.5)
Dysgeusia	11 (18.0)	0
Muscle spasms	11 (18.0)	0
Weight decreased	11 (18.0)	0
Anaemia	10 (16.4)	4 (6.6)
Cough	10 (16.4)	0
Dizziness	10 (16.4)	1 (1.6)
Diarrhoea	9 (14.8)	2 (3.3)
Headache	9 (14.8)	0
Aspartate aminotransferase increased	7 (11.5)	2 (3.3)
Blood alkaline phosphatase increased	7 (11.5)	3 (4.9)
Muscular weakness	7 (11.5)	2 (3.3)
Pyrexia	7 (11.5)	0
Asthenia	6 (9.8)	2 (3.3)
Blood bilirubin increased	6 (9.8)	1 (1.6)
Dyspnoea	6 (9.8)	3 (4.9)
Insomnia	6 (9.8)	0
Musculoskeletal chest pain	6 (9.8)	1 (1.6)
Urinary tract infection	6 (9.8)	0
Abdominal distension	5 (8.2)	0
Arthralgia	5 (8.2)	0
Dehydration	5 (8.2)	1 (1.6)
Dry mouth	5 (8.2)	0
Hyponatraemia	5 (8.2)	2 (3.3)

Preferred term	All patients N=61	
	All grades n (%)	Grade 3/4 n (%)
Night sweats	5 (8.2)	0
Fall	4 (6.6)	1 (1.6)
Hypercalcaemia	4 (6.6)	3 (4.9)
Hypokalaemia	4 (6.6)	0
Musculoskeletal pain	4 (6.6)	0
Oedema peripheral	4 (6.6)	0
Pain in extremity	4 (6.6)	0

Preferred terms are sorted in descending frequency of all grades column.
A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple adverse events is counted only once in the total row.

Adverse events with at least 5% incidence, regardless of study drug relationship, by preferred term and maximum grade – Group 2 (Safety set)

Preferred term	All patients N=51	
	All grades n (%)	Grade 3/4 n (%)
Total	50 (98.0)	28 (54.9)
Fatigue	18 (35.3)	3 (5.9)
Nausea	18 (35.3)	0
Vomiting	17 (33.3)	2 (3.9)
Decreased appetite	16 (31.4)	0
Muscle spasms	11 (21.6)	1 (2.0)
Oedema peripheral	11 (21.6)	0
Abdominal pain	9 (17.6)	2 (3.9)

Preferred term	All patients N=51	
	All grades n (%)	Grade 3/4 n (%)
Anaemia	8 (15.7)	4 (7.8)
Constipation	8 (15.7)	0
Diarrhoea	8 (15.7)	0
Dizziness	8 (15.7)	0
Myalgia	8 (15.7)	0
Back pain	7 (13.7)	1 (2.0)
Blood creatine phosphokinase increased	7 (13.7)	3 (5.9)
Arthralgia	6 (11.8)	1 (2.0)
Cough	6 (11.8)	0
Dehydration	6 (11.8)	4 (7.8)
Dyspnoea	6 (11.8)	1 (2.0)
Insomnia	6 (11.8)	0
Anxiety	5 (9.8)	0
Headache	5 (9.8)	0
Pain in extremity	5 (9.8)	1 (2.0)
Abdominal pain upper	4 (7.8)	0
Acute kidney injury	4 (7.8)	2 (3.9)
Blood alkaline phosphatase increased	4 (7.8)	2 (3.9)
Dysgeusia	4 (7.8)	0
Fall	4 (7.8)	0
Gait disturbance	4 (7.8)	0
Hypotension	4 (7.8)	0
Weight decreased	4 (7.8)	0
Abdominal distension	3 (5.9)	0

Preferred term	All patients N=51	
	All grades n (%)	Grade 3/4 n (%)
Aspartate aminotransferase increased	3 (5.9)	2 (3.9)
Asthenia	3 (5.9)	1 (2.0)
Blood bilirubin increased	3 (5.9)	2 (3.9)
Dry mouth	3 (5.9)	0
Dyspepsia	3 (5.9)	0
Flank pain	3 (5.9)	0
Hydronephrosis	3 (5.9)	2 (3.9)
Hypoalbuminaemia	3 (5.9)	0
Hyponatraemia	3 (5.9)	3 (5.9)
Hypoxia	3 (5.9)	2 (3.9)
Lipase increased	3 (5.9)	2 (3.9)
Musculoskeletal pain	3 (5.9)	0
Tachycardia	3 (5.9)	0
Urinary tract infection	3 (5.9)	0

Preferred terms are sorted in descending frequency of all grades column.
A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple adverse events is counted only once in the total row.

On-treatment deaths, by primary system organ class and preferred term – Group 1 (Safety set)

Primary system organ class Principal cause of death	All patients N=61 n (%)
Any primary system organ class	
Total	11 (18.0)
Gastrointestinal disorders	

Primary system organ class Principal cause of death	All patients N=61 n (%)
Total	1 (1.6)
Colitis	1 (1.6)
General disorders and administration site conditions	
Total	7 (11.5)
Disease progression	6 (9.8)
Death	1 (1.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Total	3 (4.9)
Adenocarcinoma pancreas	2 (3.3)
Neoplasm malignant	1 (1.6)

On-treatment deaths, by primary system organ class and preferred term – Group 2 (Safety set)

Primary system organ class Principal cause of death	All patients N=51 n (%)
Any primary system organ class	
Total	13 (25.5)
Cardiac disorders	
Total	1 (2.0)
Cardio-respiratory arrest	1 (2.0)
General disorders and administration site conditions	
Total	9 (17.6)
Disease progression	8 (15.7)
Death	1 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Total	3 (5.9)
Metastases to central nervous system	1 (2.0)
Metastatic neoplasm	1 (2.0)
Prostate cancer	1 (2.0)

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Serious adverse events, regardless of study drug relationship, by preferred term – Group 1 (Safety set)

Preferred term	All patients N=61 n (%)
Total	27 (44.3)
Anaemia	3 (4.9)
Asthenia	3 (4.9)
Vomiting	3 (4.9)
Abdominal pain	2 (3.3)
Acute kidney injury	2 (3.3)
Hyponatraemia	2 (3.3)
Nausea	2 (3.3)
Pneumonia	2 (3.3)
Acute respiratory failure	1 (1.6)
Acute sinusitis	1 (1.6)
Ascites	1 (1.6)
Atrial fibrillation	1 (1.6)
Axillary pain	1 (1.6)
Blood creatine phosphokinase increased	1 (1.6)
Cancer pain	1 (1.6)
Cellulitis	1 (1.6)
Coagulopathy	1 (1.6)
Colitis	1 (1.6)
Constipation	1 (1.6)
Decreased appetite	1 (1.6)
Dehydration	1 (1.6)
Diarrhoea	1 (1.6)
Dizziness	1 (1.6)

Preferred term	All patients N=61 n (%)
Dyspnoea	1 (1.6)
Fall	1 (1.6)
Fatigue	1 (1.6)
Gastrointestinal haemorrhage	1 (1.6)
Haematuria	1 (1.6)
Haemoptysis	1 (1.6)
Hypercalcaemia	1 (1.6)
Hypovolaemia	1 (1.6)
Lipase increased	1 (1.6)
Malignant pleural effusion	1 (1.6)
Mental status changes	1 (1.6)
Musculoskeletal chest pain	1 (1.6)
Nervous system disorder	1 (1.6)
Non-cardiac chest pain	1 (1.6)
Pneumothorax	1 (1.6)
Pseudomonas infection	1 (1.6)
Pyrexia	1 (1.6)
Renal failure	1 (1.6)
Rhabdomyolysis	1 (1.6)
Septic shock	1 (1.6)
Small intestinal obstruction	1 (1.6)
Staphylococcal infection	1 (1.6)
Tumour haemorrhage	1 (1.6)
Tumour invasion	1 (1.6)
Urosepsis	1 (1.6)

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Clinical Trial Results Database

Serious adverse events, regardless of study drug relationship, by preferred term – Group 2 (Safety set)

Preferred term	All patients N=51 n (%)
Total	18 (35.3)
Acute kidney injury	3 (5.9)
Dehydration	3 (5.9)
Hydronephrosis	2 (3.9)
Abdominal pain	1 (2.0)
Acute respiratory failure	1 (2.0)
Alanine aminotransferase increased	1 (2.0)
Anaemia	1 (2.0)
Aphasia	1 (2.0)
Arthralgia	1 (2.0)
Aspartate aminotransferase increased	1 (2.0)
Asthenia	1 (2.0)
Cardio-respiratory arrest	1 (2.0)
Confusional state	1 (2.0)
Deep vein thrombosis	1 (2.0)
Disseminated intravascular coagulation	1 (2.0)
Dysphagia	1 (2.0)
Dyspnoea	1 (2.0)
Failure to thrive	1 (2.0)
Febrile neutropenia	1 (2.0)
Gait disturbance	1 (2.0)
Haematemesis	1 (2.0)
Hemiparesis	1 (2.0)
Hypercalcaemia	1 (2.0)

Preferred term	All patients N=51 n (%)
Hypoxia	1 (2.0)
Intestinal obstruction	1 (2.0)
Muscular weakness	1 (2.0)
Obstruction gastric	1 (2.0)
Pain in extremity	1 (2.0)
Pelvic abscess	1 (2.0)
Pneumonia	1 (2.0)
Pneumonia aspiration	1 (2.0)
Pulmonary embolism	1 (2.0)
Pyelonephritis	1 (2.0)
Sepsis	1 (2.0)
Septic shock	1 (2.0)
Small intestinal obstruction	1 (2.0)
Syncope	1 (2.0)

Conclusion:

This study was conducted to evaluate the potential effect of sonidegib at a dose of 800 mg QD on the PK of the probe drugs warfarin and bupropion, which are predominantly metabolized by CYP2C9 and CYP2B6, respectively.

The study demonstrated that co-administration of sonidegib did not have effect on systemic exposures of warfarin and had no influence on the pharmacodynamics profiles of warfarin. The GMR and 90% CI for each PK parameter (AUCinf, AUClast, and Cmax) of S-warfarin and were: AUCinf: 1.15 (1.07, 1.24), AUClast: 1.14 (1.07, 1.22) and Cmax: 0.882 (0.805, 0.967) respectively and of R-warfarin were: AUCinf: 1.10 (0.979, 1.24), AUClast: 1.09 (1.03, 1.15) and Cmax: 0.928 (0.866, 0.995). These results indicate that sonidegib is not a perpetrator of drug interaction with CYP2C9 substrates.

Co-administration of sonidegib did not affect systemic exposure of bupropion. The GMR and 90% CI for each PK parameter (AUCinf, AUClast, and Cmax) of bupropion were AUClast: 1.10 (0.992, 1.23), AUCinf: 1.10 (0.987, 1.23), Cmax: 1.16 (0.952, 1.42) repectively. These results indicate that sonidegib is not a perpetrator of drug interaction with CYP2B6 substrates.

Sonidegib has an acceptable safety profile that is well characterized and consistent with previous experiences with sonidegib alone. No specific safety concerns were identified with the combination treatments, considering the severity of the underlying diseases as well as the known safety profile for each drug.

Conclusion:

Sonidegib is not a perpetrator of drug interaction with CYP2C9 substrates and CYP2B6 substrates and the combination treatment has an acceptable safety profile.

Date of Clinical Trial Report

15-Mar-2017