Sponsor

Novartis

Generic Drug Name

Dovitinib

Trial Indication(s)

Advanced solid tumors, excluding breast cancer

Protocol Number

CTKI258A2120

Protocol Title

A Phase I, multi-center, open-label, drug-drug interaction study to assess the effect of the CYP1A2 inhibitor, fluvoxamine, on dovitinib (TKI258) pharmacokinetics in patients with advanced solid tumors

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

21-May-2013 to 21-Jul-2014

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a multi-center, open-label, single-sequence, drug-drug interactions (DDI) study to assess the effect of the cytochrome P450 (CYP)1A2 inhibitor, fluvoxamine, on the pharmacokinetics (PK) of dovitinib in patients with advanced solid tumors, excluding breast cancer. The study was divided in two phases: PK and clinical treatment phase.

DDI was assessed in the PK phase of the study. A total of 45 patients enrolled in the PK phase of the study. On Day 1of the PK phase, 300 mg dovitinib was administered (5 days on/2 days off dosing schedule) to patients and continued throughout the PK phase. After 3 weeks of dovitinib dosing blood samples for dovitinib PK profiles were collected during the 72 hours

following the Day 19 dose. On Day 22 to Day 28 fluvoxamine 100 mg was administered daily to ensure continued and maximum inhibition of CYP1A2. Dovitinib was not administered on Day 27 and Day 28 as these days coincided with "off days" on the dovitinib dosing schedule. Blood samples for dovitinib PK profiles were collected during the 72 hours following the Day 26 dose of dovitinib and a single blood sample for analysis of fluvoxamine blood concentration was collected at 4 hours post dose on Day 26.

After completion of the PK phase, patients could continue to receive treatment with dovitinib at the recommended Phase II maximum tolerated dose (MTD) of 500 mg (5 days on/2 days off dosing schedule). The first dose administered was considered as Week 1 Day 1 of the clinical treatment phase and the dosing schedule of the patient was set. A trough PK sample was collected on Week 4 Day 5 during the treatment phase.

Centers

US (2), Switzerland (2), Denmark (1) and Netherlands (1).

Publication

Not applicable.

Objectives:

Primary objective: To evaluate the effect of the CYP1A2 inhibitor, fluvoxamine, on steady state PK of dovitinib in patients with advanced solid tumors, excluding breast cancer.

Secondary objectives:

- To characterize the safety and tolerability of dovitinib 300 mg followed by 500 mg, following a 5 days on/2 days off dosing schedule in patients with advanced solid tumors, excluding breast cancer.
- To describe preliminary evidence of anti-tumor activity of dovitinib in patients with advanced solid tumors, excluding breast cancer.

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

The investigational drug or study drug was dovitinib and the investigational treatments or study treatment was dovitinib and/or fluvoxamine. Dovitinib was supplied to the Investigators as 100 mg gelatin capsules by Novartis Drug Supply Management. Fluvoxamine was supplied locally by each investigative site as commercially available immediate release formulations at a total dose of dose of 100 mg. Both dovitinib and fluvoxamine were administered orally.

Statistical Methods

A formal statistical analysis was conducted to assess the relative bioavailability of dovitinib co-administered with fluvoxamine to dovitinib alone. A linear mixed effects model was fitted to the log-transformed steady state PK parameters (AUC0-72hr and Cmax). Treatment, as the

fixed effect, and patient as random effect were included in the model. For the mixed model analysis, dovitinib+fluvoxamine was the test treatment and dovitinib alone was the reference. The model-based, between-treatment mean differences (dovitinib+fluvoxamine – dovitinib alone) and the corresponding two-sided 90% confidence intervals (CIs) were calculated on the log-scale. The between-treatment differences and 90% CIs were then back transformed to the original scale to obtain the geometric mean ratios (dovitinib + fluvoxamine/dovitinib alone) and the corresponding 90% CIs.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion Criteria

- Patients diagnosed with either an advanced solid tumor, excluding breast cancer, confirmed cytopathologically or histopathologically, or advanced hepatocellular carcinoma, diagnosed according to the American Association for the Study of Liver Diseases, 2010 guidelines, which has progressed despite standard therapy, or for which no standard therapy exists.
- Age ≥ 18 years.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1.
- Patients who had the following laboratory values:
    - Absolute neutrophil count ≥ 1.5×10^9/L; Platelets ≥ 100×10^9/L; Hemoglobin ≥ 8.0 g/dL;
    - Serum creatinine ≤ 1.5×upper limit of normal (ULN) or,

      24 hours urine collection creatinine clearance ≥ 30 mL/min/1.73m^2 (≥ 50 mL/min/1.73m^2 in the presence of proteinuria) or,

      Serum creatinine >1.5-3×ULN with calculated creatinine clearance (CrCl) is ≥ 30 mL/min using the Cockcroft-Gault equation: CrCl=(140 − age in years)×(weight in kg)×(0.85 if female)/(72×serum creatinine in mg/dL)
    - Serum total bilirubin ≤ 1.5×ULN
    - Aspartate aminotransferase and alanine aminotransferase ≤ 3.0×ULN
- Urine dipstick reading: Negative for proteinuria or, if documentation of +1 results for protein on dipstick reading, then total urinary protein ≤ 500 mg and measured creatinine clearance ≥ 50 mL/min/1.73 m^3 from a 24 h urine collection.
- Patients with an anticipated life expectancy of ≥ 3 months.

Key exclusion criteria

- Patients with brain metastases as assessed by mandatory radiologic imaging (e.g., Computed Tomography; CT or Magnetic resonance imaging; MRI scan) at Screening

- Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention
- Impairment of gastrointestinal (GI) function or GI disease that might significantly alter the absorption of dovitinib.
- Patients who had received potent and moderate CYP1A2 inhibitors or potent and moderate CYP3A inhibitors within 5 days prior to starting study treatment, or are expected to receive them during the PK phase.
- Patients who had received CYP1A2 inducers (including tobacco) or CYP3A inducers within 30 days prior to starting study treatment, or were expected to receive them during the PK phase.
- Patients who were actively taking antidepressants, benzodiazepines, serotonergic drugs, and/or monoamine oxidase inhibitors.
- Patients whose alcohol intake was expected to exceed one drink per day within three days prior to the days of blood sample collection for PK assessment in the PK phase and throughout the timeframe they are taking fluvoxamine.
- Patients who were expected to consume grapefruits, pomegranates, star fruits, Seville oranges or products containing the juice of each within 3 days prior to the days of blood sample collection for PK assessment in the PK phase.
- Patients who were expected to consume homeopathic or naturopathic medicines within 5 days prior to the days of blood sample collection for PK assessment in the PK phase.
- Patients who were expected to consume non-steroidal anti-inflammatory medications and/or aspirin on days of fluvoxamine dosing.
- Pregnant or nursing (lactating) women.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using highly effective methods of contraception during dosing and for 30 days after the last dose of study medication.
- Fertile males who were not willing to use contraception.

Participant Flow Table

Patient disposition - PK phase (FAS)

Disposition	All patients N=45 n (%)
Completed	25 (55.6)
Discontinued	20 (44.4)
Adverse event	13 (28.9)
Non-compliance with study treatment	3 (6.7)

Disposition	All patients N=45 n (%)
Physician decision	1 (2.2)
Progressive disease	1 (2.2)
Protocol deviation	1 (2.2)
Subject/guardian decision	1 (2.2)

Patient disposition – Clinical treatment phase (FAS)

Disposition	All patients N=33 n (%)
Discontinued treatment	33 (100)
Primary reason for end of treatment	
Adverse event	5 (15.2)
Progressive disease	24 (72.7)
Study terminated by Sponsor	2 (6.1)
Death	2 (6.1)

Baseline Characteristics

Demographic summary (FAS)

Demographic Variable	All Patients N=45
Age (Years)	
N	45
Mean (SD)	58.3 (10.98)
Median	60.0
Minimum – Maximum	30 - 85
Age category (Years) – n (%)	
<65	31 (68.9)
≥ 65	14 (31.1)
Sex – n (%)	
Female	18 (40.0)
Male	27 (60.0)
Race – n (%)	
Caucasian	41 (91.1)
Black	2 (4.4)
Asian	2 (4.4)
Ethnicity – n (%)	
Hispanic/Latino	3 (6.7)
South Asian	2 (4.4)
Mixed ethnicity	3 (6.7)
Other	19 (42.2)
Not reported	11 (24.4)

Demographic Variable	All Patients N=45
Unknown	7 (15.6)
Weight (kg)	
N	45
Mean (SD)	79.36 (18.984)
Median	76.20
Minimum – Maximum	47.5 - 126.0
Body surface area (m^2)	
N	45
Mean (SD)	1.96 (0.277)
Median	1.99
Minimum – Maximum	1.4 - 2.6
Body mass index (kg/m^2)	
N	45
Mean (SD)	26.33 (4.956)
Median	25.89
Minimum – Maximum	19.1 - 46.2
ECOG performance status – n (%)	
0	21 (46.7)
1	24 (53.3)

BMI: body mass index
ECOG: Eastern Cooperative Oncology Group

Summary of Efficacy

Not applicable. The development of dovitinib was stopped and therefore, the Investigator decided to report only the key pharmacokinetic data and key safety data this study.

Summary of Pharmacokinetics

Summary of statistical analysis of primary PK parameters for dovitinib (PAS - dovitinib)

					Treatment comparison		
						90% CI	
PK parameter (unit)	Treatment	n	Adjusted Geo-mean	Comparison(s)	Geo-mean ratio	Lower	Upper
AUC0-72hr (hr·ng/mL)	Dovitinib	24	2880				
	Dovitinib + Fluvoxamine	24	8290	Dovitinib+Fluvoxamine: Dovitinib	2.88	2.58	3.20
Cmax (ng/mL)	Dovitinib	24	144				
	Dovitinib + Fluvoxamine	24	259	Dovitinib+Fluvoxamine: Dovitinib	1.80	1.66	1.95

PK parameter (unit)	Treatment	n	Adjusted Geo-mean	Comparison(s)	Treatment comparison Geo-mean ratio	90% CI Lower	90% CI Upper

n=number of patients with non-missing values; Geo-mean=geometric mean.

Adjusted geo-mean, Geo-mean ratio and 90% CI are all determined from a mixed effect model and back-transformed from log scale.

The model for log transformed PK parameters (AUC0-72hr and Cmax) includes treatment as a fixed factor and patient as a random factor.

Summary of dovitinib primary PK parameters by treatment (PAS - dovitinib)

Treatment	Statistics	AUC0-72hr (hr·ng/mL)	Cmax (ng/mL)
Dovitinib	n	24	24
	Mean (SD)	3180 (1470)	155 (60.9)
	CV% mean	46.3	39.3
	Geo-mean	2880	144
	CV% geo-mean	47.3	41.1
	Median	2950	154
	[Min - Max]	[1280; 7320]	[78.3; 326]
Dovitinib+Fluvoxamine	n	24	24
	Mean (SD)	9450 (4560)	281 (112)
	CV% mean	48.2	39.8
	Geo-mean	8290	259
	CV% geo-mean	59.6	44.7
	Median	7480	266
	[Min - Max]	[2620; 16300]	[106; 514]

n=Number of patients with non-missing values.

CV% = Coefficient of variation (%); CV%=(SD/mean)×100

CV% geo-mean = sqrt(exp(variance for log transformed data)−1)×100. n=Number of patients with non-missing values.

Summary of dovitinib secondary PK parameters by treatment (PAS – dovitinib)

Treatment	Statistics	AUC0-24hr (hr·ng/mL)	Cmin (ng/mL)	Tmax (hr)	Lambda_z (1/hr)	T1/2 (hr)	CLss/F (mL/hr)	Vz/F (mL)
Dovitinib	n	24	24	24	24	24	24	24
	Mean (SD)	2240 (937)	42.7 (30.7)	N/A	0.0492 (0.00701)	14.4 (1.99)	157000 (63700)	3250000 (1360000)
	CV% mean	41.8	71.9	N/A	14.2	13.8	40.5	41.7
	Geo-mean	2060	34.6	N/A	0.0487	14.2	145000	2980000
	CV% geo-mean	43.2	75.6	N/A	14.1	14.1	43.2	45.1
	Median	2200	39.3	3.97	0.0491	14.1	136000	3010000
	[Min - Max]	[1020; 4310]	[6.69; 155]	[1.90; 9.00]	[0.0387; 0.0646]	[10.7; 17.9]	[69500; 294000]	[1350000; 6010000]

Treatment	Statistics	AUC0-24hr (hr·ng/mL)	Cmin (ng/mL)	Tmax (hr)	Lambda_z (1/hr)	T1/2 (hr)	CLss/F (mL/hr)	Vz/F (mL)
Dovitinib +Fluvoxamine	n	24	19	24	19	19	19	19
	Mean (SD)	5080 (2220)	132 (76.1)	N/A	0.0359 (0.00968)	20.5 (5.06)	77300 (37200)	2120000 (782000)
	CV% mean	43.6	57.8	N/A	27.0	24.6	48.1	36.9
	Geo-mean	4600	110	N/A	0.0348	19.9	69800	2010000
	CV% geo-mean	49.9	71.9	N/A	25.9	25.9	49.1	33.8
	Median	4390	107	4.27	0.0359	19.3	72200	1970000
	[Min - Max]	[1870; 8710]	[29.6; 298]	[1.75; 9.00]	[0.0242; 0.0641]	[10.8; 28.7]	[34400; 161000]	[1120000; 4300000]

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

Summary of Safety

Safety Results

AEs, regardless of study drug relationship, by primary system organ class and maximum grade (Safety set)

	All patients (N=45)	
System Organ class	**Grade 3 / 4 n (%)**	**All grades n (%)**
Total	31 (68.9)	45 (100.0)
Gastrointestinal Disorders	12 (26.7)	41 (91.1)
General Disorders And Administration Site Conditions	12 (26.7)	32 (71.1)
Respiratory, Thoracic And Mediastinal Disorders	9 (20.0)	28 (62.2)
Nervous System Disorders	1 (2.2)	20 (44.4)
Investigations	5 (11.1)	19 (42.2)
Skin And Subcutaneous Tissue Disorders	1 (2.2)	18 (40.0)
Musculoskeletal And Connective Tissue Disorders	1 (2.2)	17 (37.8)
Infections And Infestations	5 (11.1)	15 (33.3)
Metabolism And Nutrition Disorders	4 (8.9)	15 (33.3)
Blood And Lymphatic System Disorders	2 (4.4)	9 (20.0)
Renal And Urinary Disorders	2 (4.4)	9 (20.0)
Cardiac Disorders	2 (4.4)	5 (11.1)
Psychiatric Disorders	0	5 (11.1)
Vascular Disorders	4 (8.9)	5 (11.1)
Eye Disorders	0	3 (6.7)
Hepatobiliary Disorders	0	3 (6.7)
Immune System Disorders	1 (2.2)	3 (6.7)
Injury, Poisoning And Procedural Complications	0	3 (6.7)

System Organ class	All patients (N=45) Grade 3 / 4 n (%)	All patients (N=45) All grades n (%)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	1 (2.2)	1 (2.2)
Reproductive System And Breast Disorders	0	1 (2.2)

A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
A patient with multiple grades for an AE while on a treatment, is only counted under the maximum grade.
Adverse events occurring more than 30 days after last date of study treatment are not summarized.

AEs (all grades, in >5% of patients), regardless of study drug relationship, by PT and maximum grade (Safety set)

Preferred term	All patients (N=45) Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Total	1 (2.2)	13 (28.9)	28 (62.2)	3 (6.7)	45 (100.0)
Diarrhoea	18 (40.0)	9 (20.0)	2 (4.4)	0	29 (64.4)
Fatigue	12 (26.7)	5 (11.1)	8 (17.8)	0	25 (55.6)
Nausea	14 (31.1)	9 (20.0)	1 (2.2)	0	24 (53.3)
Vomiting	12 (26.7)	5 (11.1)	2 (4.4)	0	19 (42.2)
Cough	10 (22.2)	3 (6.7)	1 (2.2)	0	14 (31.1)
Dyspnoea	8 (17.8)	3 (6.7)	2 (4.4)	1 (2.2)	14 (31.1)
Weight Decreased	4 (8.9)	8 (17.8)	0	0	12 (26.7)
Decreased Appetite	6 (13.3)	4 (8.9)	0	0	10 (22.2)
Headache	4 (8.9)	5 (11.1)	0	0	9 (20.0)
Back Pain	3 (6.7)	4 (8.9)	0	0	7 (15.6)
Constipation	4 (8.9)	3 (6.7)	0	0	7 (15.6)
Pyrexia	7 (15.6)	0	0	0	7 (15.6)
Rash	5 (11.1)	2 (4.4)	0	0	7 (15.6)
Abdominal Pain	1 (2.2)	1 (2.2)	4 (8.9)	0	6 (13.3)
Anaemia	0	6 (13.3)	0	0	6 (13.3)
Dysgeusia	6 (13.3)	0	0	0	6 (13.3)
Abdominal Pain Upper	5 (11.1)	0	0	0	5 (11.1)
Dizziness	4 (8.9)	1 (2.2)	0	0	5 (11.1)
General Physical Health Deterioration	0	2 (4.4)	2 (4.4)	0	4 (8.9)
Non-Cardiac Chest Pain	2 (4.4)	0	2 (4.4)	0	4 (8.9)
Palmar-Plantar Erythrodysaesthesia Syndrome	2 (4.4)	1 (2.2)	1 (2.2)	0	4 (8.9)
Urinary Tract Infection	0	4 (8.9)	0	0	4 (8.9)
Dermatitis Acneiform	1 (2.2)	2 (4.4)	0	0	3 (6.7)
Dry Mouth	2 (4.4)	1 (2.2)	0	0	3 (6.7)
Dyspepsia	2 (4.4)	1 (2.2)	0	0	3 (6.7)
Dysphonia	3 (6.7)	0	0	0	3 (6.7)
Facial Pain	2 (4.4)	0	1 (2.2)	0	3 (6.7)
Flank Pain	2 (4.4)	0	1 (2.2)	0	3 (6.7)

Preferred term	All patients (N=45) Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Hypertriglyceridaemia	0	0	2 (4.4)	1 (2.2)	3 (6.7)
Oedema Peripheral	3 (6.7)	0	0	0	3 (6.7)
Pain In Extremity	1 (2.2)	2 (4.4)	0	0	3 (6.7)
Stomatitis	2 (4.4)	0	1 (2.2)	0	3 (6.7)

Preferred terms are sorted by descending frequency of the all grades column.
A patient with multiple occurrences of an AE is counted only once in the AE category at maximum severity grade.
A patient with multiple adverse events is counted only once in the total row at maximum severity grade.
Adverse events occurring more than 30 days after last date of study treatment are not summarized.
AEs have been graded according to the CTCAE V4.03.

SAEs, regardless of study drug relationship, by PT, maximum grade (Safety Set)

Preferred term	All patients (N=45) Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Total	1 (2.2)	1 (2.2)	18 (40.0)	2 (4.4)	22 (48.9)
Abdominal pain	0	0	2 (4.4)	0	2 (4.4)
Dehydration	0	1 (2.2)	1 (2.2)	0	2 (4.4)
Haemoptysis	0	1 (2.2)	1 (2.2)	0	2 (4.4)
Non-cardiac chest pain	0	0	2 (4.4)	0	2 (4.4)
Pneumonia	0	0	2 (4.4)	0	2 (4.4)
Pyelonephritis	0	0	2 (4.4)	0	2 (4.4)
Vomiting	0	1 (2.2)	1 (2.2)	0	2 (4.4)
Acute coronary syndrome	0	1 (2.2)	0	0	1 (2.2)
Anuria	0	0	0	1 (2.2)	1 (2.2)
Back pain	0	1 (2.2)	0	0	1 (2.2)
Diarrhoea	0	0	1 (2.2)	0	1 (2.2)
Dizziness	0	1 (2.2)	0	0	1 (2.2)
Epilepsy	0	0	1 (2.2)	0	1 (2.2)
Fatigue	0	0	1 (2.2)	0	1 (2.2)
Febrile neutropenia	0	0	1 (2.2)	0	1 (2.2)
General physical health deterioration	0	0	1 (2.2)	0	1 (2.2)
Haematuria	0	0	1 (2.2)	0	1 (2.2)
Headache	0	1 (2.2)	0	0	1 (2.2)
Hiccups	0	0	1 (2.2)	0	1 (2.2)
Intestinal obstruction	0	0	1 (2.2)	0	1 (2.2)
Multi-organ failure	0	0	0	1 (2.2)	1 (2.2)
Nausea	1 (2.2)	0	0	0	1 (2.2)
Oesophageal stenosis	0	1 (2.2)	0	0	1 (2.2)
Oliguria	0	0	0	1 (2.2)	1 (2.2)
Peritonitis bacterial	0	0	1 (2.2)	0	1 (2.2)
Pleural effusion	0	0	0	1 (2.2)	1 (2.2)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	All patients (N=45) Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Pulmonary embolism	0	0	1 (2.2)	0	1 (2.2)
Pyrexia	1 (2.2)	0	0	0	1 (2.2)
Respiratory failure	0	0	0	1 (2.2)	1 (2.2)
Sepsis	0	0	1 (2.2)	0	1 (2.2)
Thrombosis	0	0	1 (2.2)	0	1 (2.2)
Tumour pain	0	0	1 (2.2)	0	1 (2.2)
Upper gastrointestinal haemorrhage	0	0	1 (2.2)	0	1 (2.2)
Upper respiratory tract infection	0	0	1 (2.2)	0	1 (2.2)

Preferred terms are sorted by descending frequency of the all grades column.
A patient with multiple occurrences of an AE is counted only once in the AE category at maximum severity grade.
A patient with multiple adverse events is counted only once in the total row at maximum severity grade.
Adverse events occurring more than 30 days after last date of study treatment are not summarized.
AEs have been graded according to the CTCAE V4.03

On-treatment death, by primary SOC, and PT (Safety Set)

Primary system organ class **Principal cause of death**	**All patients N=45 n (%)**
Any Primary System Organ Class-Total	6 (13.3)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps) -Total	6 (13.3)
Neoplasm	6 (13.3)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class by descending frequency.
Deaths up to 30 days after the last dose are all included.

Other Relevant Findings

Not applicable

Conclusion:

- Administration of multiple doses of the CYP1A2 inhibitor, fluvoxamine, with dovitinib showed a weak to moderate inhibitory effect on dovitinib metabolism in patients with advanced solid tumors, excluding breast cancer
- No new safety concerns were identified in this study with dovitinib at a dose of 300 mg and 500 mg (with 5 days on/ 2 days off dosing schedule).

Date of Clinical Trial Report

17 Jun 2015

Date of Initial Inclusion on Novartis Clinical Trial Results website

01-Jul-2015

Date of Latest Update

Not applicable

Reason for Update

Not applicable