Sponsor

Novartis Pharmaceuticals.

Generic Drug Name

Dovitinib

Therapeutic Area of Trial

Advanced Solid Tumor Malignancies

Approved Indication

Investigational

Study Number

CTKI258A2106

Title

An open-label, non-randomized, single-center, phase I study to determine the absorption, distribution, metabolism and excretion (ADME) of Dovitinib after a single oral administration of Dovitinib 500 mg and to assess preliminary safety of Dovitinib 400 mg once daily in patients with advanced solid tumor malignancies.

Phase of Development

Phase I

Study Start/End Dates

08 Apr 2008 to 04 Jan 2010

Study Design/Methodology

The study started with Cohort 1 Period 1 (core phase): a screening/baseline period of up to 3 weeks, followed by a single dose of [^{14}C] Dovitinib and sample collection period of at least 168 hours (Day 1 through Day 8), followed by 1 week wash-out phase. On Day 1, patients received 5 capsules containing 100 mg [^{14}C] Dovitinib for each capsule with a total of 500 mg [^{14}C] Dovitinib, i.e. 1.85 MBq (50µCi) of radioactivity as a single oral administration. Blood was collected during the 168 hours following the dose administration. Complete urinary and fecal output was collected over the same 168 hour period. Any vomitus occurring within the eight hours immediately following the dose administration was also collected. If vomitus occurred within four hours of dose administration, the patient was replaced and no re-dosing with [^{14}C] Dovitinib of the same patient was permitted. If radioactivity recovered in vomitus in such a patient was ≥ 85% of the total administered radioactivity, the patient could be discharged. If radioactivity recovered in vomitus was < 85% of total administered radioactivity, the radioactivity in urine and feces produced by this patient was measured and monitored until ≥ 85% of the total administered radioac-

tivity has been recovered, at which time the patient could be discharged. Upon the investigator's discretion, patients could return on Day 16 to start their non-radiolabeled Dovitinib treatment.

Patients returning on Day 16 to the study site were assessed, and if found eligible, were offered to continue in Cohort 1 Period 2 (extension phase): continuous daily dosing with 400 mg Dovitinib in 28 day cycles. Patients were treated until disease progression or unacceptable toxicity.

In cohort 2, patients were evaluated for safety and preliminary efficacy as outlined in Cohort 1 Period 2.

Centres

1 centre in the Netherlands

Publication

None

Objectives

Primary objective(s):

Cohort 1

- To determine the rates and routes of excretion of Dovitinib and its metabolites, including mass balance in urine and feces after a single oral dose of radiolabeled ^{14}C Dovitinib to patients
- To determine the pharmacokinetics of total radioactivity in blood and plasma
- To determine the pharmacokinetics of Dovitinib in plasma
- To quantify and characterize the structures of the metabolites of Dovitinib in plasma, urine and feces in order to elucidate the biotransformation pathways

Cohort 2

- To assess preliminary safety of Dovitinib 400 mg once daily dosing

Secondary objective(s):

Cohort 1

- To explore the safety and tolerability of Dovitinib in patients with solid malignancies
- To explore the preliminary anti-tumor activity of Dovitinib in patients with solid malignancies

Cohort 2

- To explore the preliminary anti-tumor activity of Dovitinib in patients with solid malignancies

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

Cohort 1 Period 1:

500 mg [^{14}C] Dovitinib (5 capsules with 100 mg per capsule) were administered early in the morning on Day 1..

Cohort 1 Period 2 and all patients in Cohort 2:

Once daily continuous dosing of non-radiolabeled 400 mg Dovitinib (4 capsules with 100 mg per capsule) on Day 16 or Cycle 1 Day 1.

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

Not applicable.

Criteria for Evaluation

Primary variables:

Determination of mass balance, metabolite profiles, and pharmacokinetic variables:

Blood was collected from the patients at fixed time points following the [^{14}C] Dovitinib dose. The radioactivity in blood and plasma at each time point was measured using liquid scintillation counting and pharmacokinetic parameters were determined for blood and plasma.

All urine and feces produced by the four patients from pre-dose and up to 240 h (10 days) following administration of Dovitinib were collected. The radioactivity associated with each urine or feces sample was measured and the percentage of the dose excreted was calculated.

Plasma was assayed for Dovitinib using a validated liquid chromatography-mass spectrometry (LC-MS) method and pharmacokinetic parameters were determined.

Plasma, urine, and feces were investigated for metabolite profiles using liquid chromatography with radioactivity detection. Metabolite structures were elucidated using mass spectrometry.

Secondary variables:

Safety and tolerability

Frequency of adverse events, laboratory abnormalities, and other tests (e.g., vital signs, Electrocardiogram [ECG]).

Efficacy

Overall response by modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria for the efficacy evaluation. Baseline tumor assessment was performed within approximately 28 days and follow up evaluations were assessed every 8 weeks (± 3 days) to determine response.

Statistical Methods

Only summary statistics were provided and formal statistics were not performed as the study was not powered for such evaluations.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Age ≥ 18
- World Health Organization (WHO) Performance Status Score of ≤ 2;
- All of the following laboratory parameters:
  - Absolute neutrophil count (ANC) ≥ 1,500/mm^3(SI units 1.5 x 10^9/L)
  - Platelets ≥ 75,000/mm^3(SI units 75 x 10^9/L)

- Hemoglobin ≥ 8.0 g/dL [SI units 80 g/L]
- Serum creatinine < 1.5 x upper limit of normal (ULN) or creatinine clearance > 60 ml/min,
- Bilirubin ≤ 1.5 ULN,
- AST (SGOT) and ALT (SGPT) ≤ 2.5 x ULN except for patients with tumor involvement of the liver who must have AST and ALT ≤ 5 x 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/1.73m$_3$ from a 24 hour urine collection.

Exclusion Criteria:

- All previous treatment (including surgery and radiotherapy) must have been completed at least four weeks prior to study entry and any acute toxicities must have been resolved
- Any treatment with investigational drugs within 30 days before the start of the study
- Pregnant or lactating women (all women of childbearing potential (WOCBP) must have a negative pregnancy test (> 5 mIU/mL) before inclusion in the study; post-menopausal women must be amenorrheic for at least 12 months). Female patients must use adequate contraceptive protection. Healthy female subjects between 18 – 65 years of age who are post-menopausal or sterile as defined by any of the following:
  - Subjects at least 50 years of age and amenorrheic for at least 12 months or
  - Subjects under 50 years of age and amenorrheic for at least 2 years or
  - Prior documented bilateral oophorectomy or tubal ligation and not receiving hormonal replacement therapy, and show no clinically significant deviation from normal in medical history, physical examination, vital signs, cardiograms, and clinical laboratory determinations.
  - Must be confirmed by a plasma 17β-estradiol concentration of < 20 pg/mL and a plasma FSH level of > 40 IU/L
- Fertile males not willing to use contraception or whose female partners are not using adequate contraceptive protection
- Clinically significant cardiac impairment or unstable ischemic heart disease including a myocardial infarction within six months of study start
- Centrally located or squamous cell carcinoma of the lung
- Uncontrolled infections
- Surgery involving intestinal anastomosis within four weeks of study start
- History of gastrointestinal malabsorption
- Primary brain tumors or symptomatic leptomeningeal metastases
- Known diagnosis of HIV infection (HIV testing is not mandatory)
- History of alcoholism, drug addiction, or any psychiatric or psychological condition which, in the opinion of the investigator, would impair study compliance
- Legal incapacity

Number of Subjects

Patient disposition (Full analysis set):

	Cohort 1			Cohort 2
	Core phase	Extension phase	Total	All patients
	(N=4)	(N=3)	(N=4)	(N=9)
	n (%)	n (%)	n (%)	n (%)
Enrolled	4(100.0)	n/a	4(100.0)	9(100.0)
Completed period 1 (core)	4(100.0)	n/a	4(100.0)	n/a
Entered period 2 (extension)	3 (75.0)	n/a	3 (75.0)	n/a
End of treatment				
Primary reason for end of treatment				
Disease progression	1 (25.0)	3(100.0)	4(100.0)	9(100.0)

Demographic and Background Characteristics

Demographic Variable	Cohort 1 All Patients (N=4)	Cohort 2 All Patients (N=9)
Age (Years)		
n	4	9
Mean	51.0	51.0
SD	6.83	15.34
Median	50.0	53.0
Min	44	24
Max	60	66
Sex		
Male	1(25.0)	6(66.7)
Female	3(75.0)	3(33.3)
Race		
Caucasian	4(100.0)	9(100.0)
Black	0	0
Asian	0	0
Native American	0	0
Pacific Islander	0	0
Other	0	0
Weight (kg)		
n	4	6[a]
Mean	67.63	90.00
SD	15.041	11.815

Median	73.50	92.00
Min	45.5	71.0
Max	78.0	105.0
Height (cm)		
n	4	6[b]
Mean	171.3	180.2
SD	2.87	11.60
Median	170.5	178.5
Min	169	168
Max	175	194
BMI (kg/m^2)[1]		
n	4	6
Mean	23.03	27.78
SD	5.041	3.442
Median	24.45	27.05
Min	15.9	24.6
Max	27.3	34.0
Baseline WHO performance status [2, c]		
0	1(25.0)	3(33.3)
1	2(50.0)	5(55.6)
2	1(25.0)	0

[1] Body Mass Index (BMI): [kg/m^2] = weight[kg] / (height[m]^2)

[2] WHO performance status:

0 = Fully active, able to carry on all pre-disease performance without restriction.

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.

2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

In Cohort 2:

[a] Three patients had no baseline weight recorded in the database. Of these 3, 2 patients had the weight assessed on Day 1 of the study (day of the first dose), 1 patient weight was not assessed.

[b] Three patients had no height data recorded in the database.

[c] One patient whose performance status was “0” on Day 1 of the study (day of the first dose) was not included in the table.

Primary Objective Result(s)

Excretion of radioactivity in urine and feces following a single oral 500 mg dose of [^{14}C] Dovitinib:

	Dose Recovery (%)					
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Mean**	**SD**
Urine	20.7	16.9	15.4	12.6	16.4	3.4
Feces	52.4	68.5	63.3	1.5	46.4	30.7
Feces Patients 1,2, and 3					61.4	8.2

Total dose recovery in excreta	73.1	85.4	78.7	14.1	62.8	32.9
Total Patients 1, 2, and 3					79.1	6.2

COHORT 1:

Pharmacokinetic parameters for total radioactivity in blood:

Patient	T_{max} (hr)	C_{max} (ngEq/mL)	AUC_{0-24} (hr*ngEq/mL)	AUC_{last} [a] (hr*ngEq/mL)	AUC_{inf} (hr*ngEq/mL)	T1/2 [b] (hr)
1	48	923	14900	83600	94700	41.1
2	7	661	11500	28900	29300	29.9
3	3	990	13700	42000	44500	38.9
4	7	761	14200	40500	47400	69.7
Mean		834	13600	48800	54000	44.9
SD		150	1490	23900	28300	17.2
Median	7	842	14000	41300	46000	39.6

[a] The last measured sample time (T_{last}) was 144 h for Patient 1. For Patients 2, 3, and 4, T_{last} was168h.
[b] $T_{1/2}$ determination used the time range 72 – 168 hr (72-144 hr for patient 1).

Pharmacokinetic parameters for total radioactivity in plasma:

Patient	T_{max} (hr)	C_{max} (ngEq/mL)	AUC_{0-24} (hr*ngEq/mL)	AUC_{last} [a] (hr*ngEq/mL)	AUC_{inf} (hr*ngEq/mL)	T1/2 [b] (hr)
1	48	1210	12900	101000	119000	51.8
2	5	704	11600	40100	48400	68.9
3	3	831	14200	57900	66700	53.8
4	7	567	11300	41300	48100	58.4
Mean		828	12500	60100	70500	58.2
SD		276	1320	28600	33300	7.66
Median	6	768	12300	49600	57500	56.1

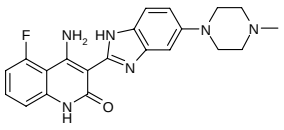
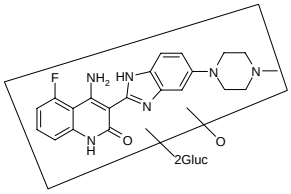
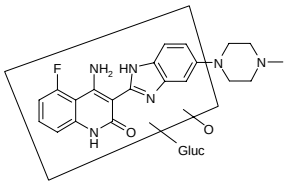
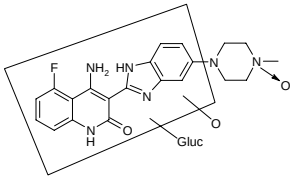
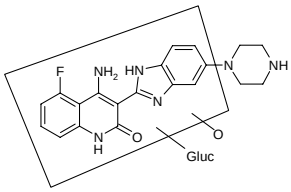
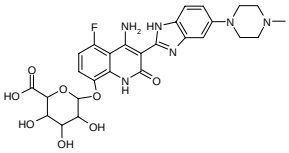
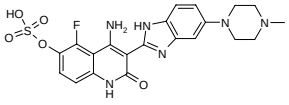
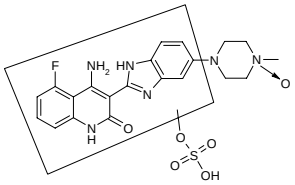
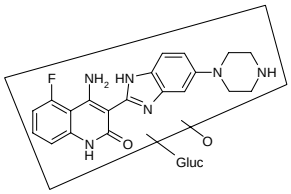
[a] T_{last} was 168 h for all patients
[b] $T_{1/2}$ determination used the time range 120 – 168 hr

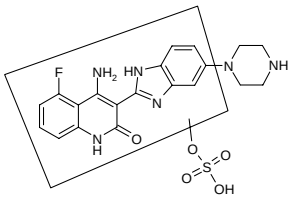
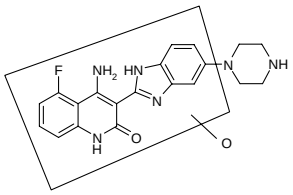
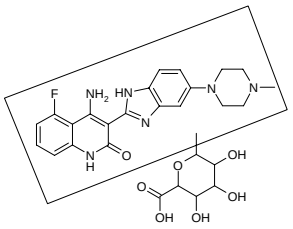
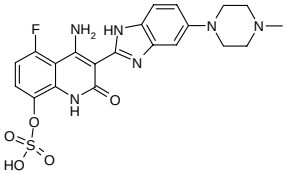
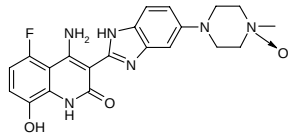
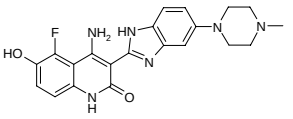
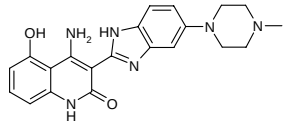
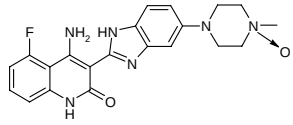
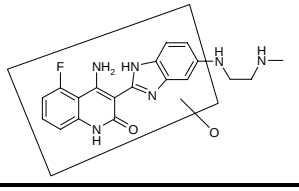
Pharmacokinetic parameters for Dovitinib in plasma:

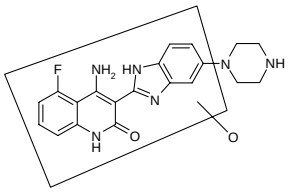
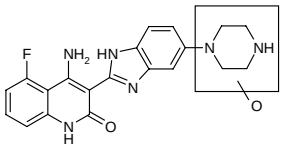
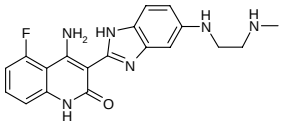
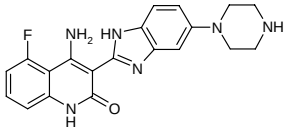
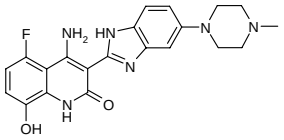
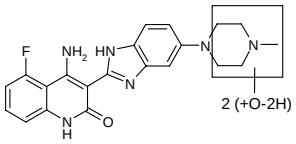
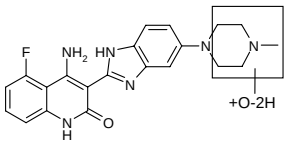
Patient	Tmax (hr)	Cmax (ng/mL)	AUC_{0-24} (hr*ng/mL)	AUC_{last} [a] (hr*ng/mL)	AUC_{inf} (hr*ng/mL)	Lamda_z [b] (1/hr)	$T_{1/2}$ (hr)	CL/F (L/hr)	Vz/F (L)
1	3	410	5320	7930	8030	0.014	49.5	62.2	4450
2	5	643	9080	15100	15100	0.031	22.6	33.1	1080
3	3	696	8870	14800	14900	0.027	26.0	33.6	1260
4	5	444	7550	12000	12000	0.023	30.5	41.6	1830
Mean		548	7710	12500	12500	0.024	32.2	42.6	2160
SD		142	1730	3330	3300	0.007	12.0	13.6	1560
Median	4	544	8210	13400	13500	0.025	28.3	37.6	1550

[a] T_{last} = 144 h for Patient 2, 168 h for Patients 1, 3, and 4.
b Lambda_z and $T_{1/2}$ determination used the time range 96– 168 hr (96-144 hr for patient 2)

Proposed structures of Dovitinib metabolites in patients following a single oral dose of 500 mg [^{14}C] Dovitinib:

~ RT [a] (min)	Exact mass MH^+ *m/z*	Measured mass MH^+ *m/z*	Mass error (ppm)	Matrix	Proposed structures
33.7	393.1834	393.1845	2.8	feces, plasma, urine	
13.1	761.2425	761.2438	1.7	urine	
14.3	585.2104	585.2062	-7.2	Urine	
15.9	601.2053	601.2065	2.0	urine	
17.8	571.1947	571.1912	-6.1	Urine	
19.6	585.2104	585.2113	1.5	Feces, urine	
20.4	489.1351	489.1363	2.5	Feces, urine	
20.8	505.1300	505.1309	1.8	Plasma, urine	
21	571.1947	571.1958	1.9	urine	

23.2	475.1194	475.1207	2.7	Feces, urine	
23.4	395.1626	395.1608	4.6	Feces, urine (trace)	
24.2	569.2155	569.2166	1.9	Feces, plasma, urine	
24.9	489.1351	489.1364	2.7	Feces, Plasma, urine	
25	425.1732	425.1744	2.8	Feces (trace), urine	
25.7	409.1783	409.1795	2.9	Feces, Urine	
26.3	391.1877	391.1890	3.3	Feces	
27	409.1783	409.1799	3.9	Plasma, urine	
27.5	383.1626	383.1638	3.1	Feces	

28	395.1626	395.1641	3.8	Feces, urine (trace)	
29	395.1626	395.1639	3.3	Feces, urine	
29.2	367.1677	367.1688	3.0	Feces, plasma, urine	
29.7	379.1677	379.1690	3.4	Feces, plasma, urine	
30.9	409.1783	409.1798	3.7	Feces, urine	
32.1	421.1419	421.1417	-0.2	feces	
37.6	407.1626	407.1624	-0.2	feces	

COHORT 2:

Adverse events, regardless of study drug relationship, by primary system organ class, preferred term (Safety set):

	Cohort 1			Cohort 2
Primary system organ class Preferred term	**Core phase* (N=4) n (%)**	**Extension phase* (N=3) n (%)**	**Total (N=4) n (%)**	**All Patients (N=9) n (%)**
- Any primary system organ class				
- Total	4(100.0)	3(100.0)	4(100.0)	9(100.0)
Blood and Lymphatic System Disorders				
- Total	0	0	0	1 (11.1)
Anaemia	0	0	0	1 (11.1)
Eye Disorders				
- Total	1 (25.0)	0	1 (25.0)	2 (22.2)

Eye Irritation	0	0	0	1 (11.1)
Eye Pain	0	0	0	1 (11.1)
Vision Blurred	1 (25.0)	0	1 (25.0)	0
Gastrointestinal Disorders				
- Total	4(100.0)	3(100.0)	4(100.0)	9(100.0)
Nausea	3 (75.0)	2 (66.7)	3 (75.0)	9(100.0)
Vomiting	3 (75.0)	2 (66.7)	3 (75.0)	7 (77.8)
Constipation	1 (25.0)	2 (66.7)	3 (75.0)	5 (55.6)
Diarrhoea	2 (50.0)	2 (66.7)	3 (75.0)	4 (44.4)
Abdominal Pain	0	0	0	2 (22.2)
Dry Mouth	0	0	0	2 (22.2)
Stomatitis	1 (25.0)	1 (33.3)	1 (25.0)	2 (22.2)
Haemorrhoids	0	0	0	1 (11.1)
Dyspepsia	0	1 (33.3)	1 (25.0)	0
Gastrointestinal Haemorrhage	0	1 (33.3)	1 (25.0)	0
Haematemesis	0	1 (33.3)	1 (25.0)	0
General Disorders and Administration Site Conditions				
- Total	3 (75.0)	3(100.0)	4(100.0)	6 (66.7)
Fatigue	2 (50.0)	2 (66.7)	3 (75.0)	5 (55.6)
Pyrexia	0	0	0	3 (33.3)
Oedema Peripheral	1 (25.0)	0	1 (25.0)	2 (22.2)
Chills	0	0	0	1 (11.1)
Malaise	0	0	0	1 (11.1)
Systemic Inflammatory Response Syndrome	0	0	0	1 (11.1)
General Physical Health Deterioration	1 (25.0)	0	1 (25.0)	0
Generalised Oedema	0	1 (33.3)	1 (25.0)	0
Pitting Oedema	0	1 (33.3)	1 (25.0)	0
Hepatobiliary Disorders				
- Total	0	0	0	1 (11.1)
Cholangitis	0	0	0	1 (11.1)
Infections and Infestations				
- Total	0	1 (33.3)	1 (25.0)	2 (22.2)
Nasopharyngitis	0	0	0	2 (22.2)
Urinary Tract Infection	0	1 (33.3)	1 (25.0)	1 (11.1)
Injury, Poisoning and Procedural Complications				
- Total	0	0	0	1 (11.1)
Spinal Cord Injury	0	0	0	1 (11.1)
Investigations				
- Total	0	1 (33.3)	1 (25.0)	5 (55.6)
Alanine Aminotransferase Increased	0	0	0	4 (44.4)
Aspartate Aminotransferase Increased	0	0	0	3 (33.3)
Blood Alkaline Phosphatase Increased	0	0	0	2 (22.2)
Gamma-glutamyltransferase Increased	0	0	0	2 (22.2)
Blood Bilirubin Increased	0	0	0	1 (11.1)

C-reactive Protein Increased	0	0	0	1 (11.1)
Weight Decreased	0	0	0	1 (11.1)
Blood Albumin Decreased	0	1 (33.3)	1 (25.0)	0
Haemoglobin Decreased	0	1 (33.3)	1 (25.0)	0
Metabolism and Nutrition Disorders				
- Total	0	1 (33.3)	1 (25.0)	1 (11.1)
Anorexia	0	0	0	1 (11.1)
Dehydration	0	1 (33.3)	1 (25.0)	0
Hypocalcaemia	0	1 (33.3)	1 (25.0)	0
Hypophagia	0	1 (33.3)	1 (25.0)	0
Musculoskeletal and Connective Tissue Disorders				
- Total	1 (25.0)	0	1 (25.0)	4 (44.4)
Arthralgia	1 (25.0)	0	1 (25.0)	1 (11.1)
Back Pain	0	0	0	1 (11.1)
Flank Pain	0	0	0	1 (11.1)
Musculoskeletal Chest Pain	0	0	0	1 (11.1)
Neoplasms Benign, Malignant and Unspecified				
- Total	0	0	0	2 (22.2)
Cancer Pain	0	0	0	2 (22.2)
Nervous System Disorders				
- Total	0	0	0	3 (33.3)
Neuropathy Peripheral	0	0	0	2 (22.2)
Dizziness	0	0	0	1 (11.1)
Dysgeusia	0	0	0	1 (11.1)
Headache	0	0	0	1 (11.1)
Psychiatric Disorders				
- Total	1 (25.0)	0	1 (25.0)	0
Insomnia	1 (25.0)	0	1 (25.0)	0
Mood Altered	1 (25.0)	0	1 (25.0)	0
Renal and Urinary Disorders				
- Total	0	1 (33.3)	1 (25.0)	1 (11.1)
Pollakiuria	0	0	0	1 (11.1)
Renal Impairment	0	1 (33.3)	1 (25.0)	0
Respiratory, Thoracic and Mediastinal Disorders				
- Total	0	2 (66.7)	2 (50.0)	5 (55.6)
Dyspnoea	0	1 (33.3)	1 (25.0)	3 (33.3)
Cough	0	1 (33.3)	1 (25.0)	2 (22.2)
Atelectasis	0	0	0	1 (11.1)
Epistaxis	0	0	0	1 (11.1)
Increased Upper Airway Secretion	0	1 (33.3)	1 (25.0)	0
Oropharyngeal Pain	0	1 (33.3)	1 (25.0)	0
Productive Cough	0	1 (33.3)	1 (25.0)	0
Skin and Subcutaneous Tissue Disorders				
- Total	0	0	0	7 (77.8)
Rash	0	0	0	4 (44.4)

Dry Skin	0	0	0	1 (11.1)
Erythema	0	0	0	1 (11.1)
Hyperhidrosis	0	0	0	1 (11.1)
Vascular Disorders				
- Total	0	1 (33.3)	1 (25.0)	1 (11.1)
Hypertension	0	0	0	1 (11.1)
Jugular Vein Thrombosis	0	1 (33.3)	1 (25.0)	0

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class by descending order of frequencies.

A patient with multiple occurrences of an AE in one phase is counted only once in the AE category for that phase. A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

For Cohort 1, if an AE occurred after taking study drug in period x and prior to taking the study drug in period x (or up to the end of study), this AE will be accounted for under the treatment given in period x.

* Core phase = Period 1 (single dose of 500 mg [^{14}C] Dovitinib); Extension phase = Period 2 (continuous daily dosing of 400 mg non-radiolabeled Dovitinib).

Secondary Objective Result(s)

Efficacy:

Of the thirteen patients enrolled in the study (4 in Cohort 1, 9 in Cohort 2), ten patients (2 in Cohort 1, 8 in Cohort 2) had both baseline and follow-up tumor assessment. Investigator overall response of PR (unconfirmed) was observed for one patient

Safety Results

Adverse Events by System Organ Class

Data are presented under the Primary Objective Results.

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

Two patients discontinued treatment due to AEs due to grade 2 hypocalcaemia (suspected) and grade 3 general physical health deterioration (not suspected).

Serious Adverse Events and Deaths

Five patients experienced SAEs during the study which included grade 3 gastrointestinal haemorrhage (not suspected)/ grade 3 stomatitis (suspected), grade 3 nausea (suspected)/ grade 3 vomiting (suspected), grade 3 general physical health deterioration (not suspected), grade 3 cholangitis (not suspected), and grade 3 spinal cord injury (not suspected).

Two patients discontinued treatment due to AEs which included grade 2 hypocalcaemia (suspected) and grade 3 general physical health deterioration (not suspected).

Date of Clinical Trial Report

12 Oct 2011

Date Inclusion on Novartis Clinical Trial Results Database

22 Dec 2011

Date of Latest Update