Sponsor

Novartis

Generic Drug Name

Dovitinib

Trial Indication(s)

Advanced solid tumors

Protocol Number

CTKI258A2116

Protocol Title

A randomized, open-label, multi-center, Phase I, crossover study to assess the relative bioavailability of 2 oral formulations of TKI258 (CSF capsule vs. FMI tablet), and the effect of food on the bioavailability of TKI258, in patients with advanced solid tumors

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase II

Study Start/End Dates

06-Jul-2010/01-Nov-2013

Primary analysis data cut-off date: 14-Mar-2012 (six patients were still continuing in the study at the time of the primary analysis cut-off date: three patients were still receiving treatment with dovitinib, and three patients had ended treatment with dovitinib but were still being followed up for safety, tumor assessment, and study evaluation completion assessments).

Reason for Termination (If applicable)

Not applicable.

Study Design/Methodology

This trial was a Phase I, two-arm, open-label, randomized, multi-center, crossover trial to compare the relative bioavailability of the CSF capsule and FMI tablet formulations of dovitinib (Arm 1), and the effect of food on the bioavailability of a preferred formulation (CSF or FMI) of dovitinib (Arm 2), in patients with advanced solid tumors, excluding breast cancer.

Each arm of the study used a crossover design during Cycle 1 of treatment:

- For Arm 1, Cycle 1, dovitinib was administered as a single 500-mg dose of either the CSF capsule or FMI tablet formulation, followed by 7 days of rest, and then a single 500-mg dose of the other formulation, followed by 2 to 9 days of rest. In Arm 2, Cycle 1, the effect of food on dovitinib, administered as the preferred formulation from Arm 1 (FMI tablet), was assessed under three prandial conditions (low fat (LF), high fat (HF), or no meal (NM)) with patients randomized to 1 of 6 treatment sequences. Dovitinib 300-mg was administered with continuous daily dosing.
- For all subsequent cycles, dovitinib was administered as a single 500-mg dose on a 5 days on/2 days off schedule, to be repeated every 7 days as part of 28-day treatment cycles. For these subsequent cycles, Arm 1 used the CSF formulation and Arm 2 used the FMI formulation.

Centers

4 centers in the USA

Publication

None

Objectives:

The primary objectives were:

- To determine the relative bioavailability of the FMI form of dovitinib (monohydrate tablets) as compared to the CSF of dovitinib (anhydrate capsules), in patients with advanced solid tumors, excluding breast cancer (Arm 1)
- To determine the effect of food on the bioavailability of dovitinib in patients with advanced solid tumors, excluding breast cancer (Arm 2)

The secondary objectives were:

- To characterize the safety and tolerability of dovitinib, including acute and chronic toxicities, in patients with advanced solid tumors, excluding breast cancer
- To evaluate the 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

Dovitinib was supplied by Novartis Drug Supply Management to the investigative sites/institutions as 100-mg hard-gelatin capsules for the CSF (anhydrate) formulation and as 250-mg and 100-mg tablets in the FMI (monohydrate) formulation. Patients were to take their once-daily dose of dovitinib in the morning. However, on days of PK sampling, patients were to bring their dose of dovitinib to the investigative site where administration of dovitinib would be supervised by a member of the research team.

Statistical Methods

The PK set was used for all model analysis and summary statistics. Summary statistics including n, arithmetic mean, standard deviation (SD), coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum and maximum were presented for dovitinib plasma concentrations for each treatment at each scheduled time point. The arithmetic mean (SD) and individual plasma concentration versus time profiles were displayed graphically using both a linear and semi-logarithmic view. All concentration data

were listed using the randomized set. A formal statistical analysis was performed to estimate the relative bioavailability of dovitinib (FMI tablet formulation) compared with the CSF capsule formulation. A linear mixed effects model was fitted to the log-transformed PK parameters (AUClast, AUCinf, and Cmax for Arm 1; and AUClast and Cmax for Arm 2). Included in the model were treatment (Arm 1) or food state (Arm 2), period, and sequence as fixed factors and subjects nested within sequences as a random factor.

For the bioavailability analysis (Arm 1), the FMI tablet formulation was the test and the intact CSF capsule formulation was the reference. For the food effect analysis (Arm 2), LF and HF food states were the test treatments and NM was considered the reference. The two-sided 90% confidence interval (CI) for the least square means of the difference (test – reference) on the log-scale was calculated. This was anti-logged to obtain the point estimates and the 90% confidence interval for the ratio of the geometric means on the untransformed scale. Descriptive statistics were presented for all PK parameters by treatment. Along with simple summary statistics (n, arithmetic mean, SD, median, minimum, maximum), CV (%) for arithmetic mean, geometric mean, and CV (%) for geometric mean were presented. For Tmax, median, minimum, and maximum were presented.

An interim analysis of PK data for Arm 1 was conducted when at least 16 evaluable patients had completed Cycle 1 of Arm 1. Based on the results of the bioavailability test from Arm 1 a preferred formulation (CSF or FMI) was then chosen for Arm 2 (food effect) of the study. An interim analysis of PK data for Arm 2 was conducted when at least 18 evaluable patients had completed Cycle 1 of Arm 2 to understand the effect of food on PK exposure of dovitinib.

Demographics and baseline characteristics were summarized for the randomized set using descriptive statistics for both arms, and additionally for the PK set for Arm 2. Relevant medical histories and continuing medical conditions were summarized by primary system organ class (SOC), preferred term (PT), and treatment sequence for the randomized set.

All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 15.0) that consisted of the SOC and PT information.

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used to grade the severity of adverse events.
The incidences of treatment-emergent AEs were summarized by system organ class and preferred term. AEs that resulted in treatment discontinuation and serious AEs (SAEs) were listed for Cycle 1 and subsequent cycle separately. Deaths were listed for all cycles combined.

Study Population: Key Inclusion/Exclusion Criteria

Patients ≥ 18 years of age, with cytopathologically- or histopathologically-confirmed diagnosis of an advanced solid tumor (excluding breast cancer) who progressed despite standard therapy, or for which no standard therapy existed, were enrolled in this trial. Patients with advanced solid tumors were an appropriate population because dovitinib has demonstrated activity in multiple preclinical models of diverse tumor origin, and preliminary evidence suggests clinical activity, including objective responses, in patients with metastatic renal cell carcinoma.

Other major inclusion criteria were:

- World Health Organization (WHO) performance status (PS) ≤ 2
- Patient must have had the following laboratory values:
  - Absolute neutrophil count (ANC) ≥ 1.5 x 109/L
  - Platelets ≥ 75 x 109/L
  - Hemoglobin ≥ 9.0 g/dL
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x upper limit of normal (ULN) (with or without liver metastases)
  - Serum bilirubin ≤ 1.5 x ULN
  - Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 50 mL/min (based on Cockcroft-Gault formula)

Major exclusion criteria were:

- Patients with a history of primary central nervous system tumors or brain metastases or who have signs/symptoms attributable to brain metastases and have not been assessed with radiologic imaging to rule out the presence of brain metastases
- Any of the following concurrent severe and/or uncontrolled medical conditions which could have compromised participation in the study:
  - Impaired cardiac function or clinically significant cardiac diseases
  - Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of dovitinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)

- Cirrhosis, chronic active hepatitis or chronic persistent hepatitis. Note: patients with study indication sites of disease in the liver are eligible provided all inclusion/exclusion criteria are met, and the patient is classified, by the Child-Turcotte-Pugh Scoring System, as Class A
- Acute or chronic renal disease. Note: patients with study indication sites of disease in the kidney are eligible provided all inclusion/exclusion criteria are met
- Other concurrent severe and/or uncontrolled concomitant medical conditions

Participant Flow Table

Patient disposition: Primary data cut-off (14-Mar-2012)

Patient disposition by treatment sequence in Arm 1 - Cycle 1 (Randomized set)

Disposition	CSF/FMI N=10 n (%)	FMI/CSF N=11 n (%)	All Patients N=21 n (%)
Ongoing[†]	**8 (80.0)**	**11 (100.0)**	**19 (90.5)**
Discontinued[†]	**2 (20.0)**	**0**	**2 (9.5)**
Primary reason for end of treatment			
Adverse event	1 (10.0)	0	1 (4.8)
Patient withdrew consent	1 (10.0)	0	1 (4.8)

[†] Includes all randomized patients who are ongoing or discontinued prior to Cycle 2
CSF=Clinical service form; FMI=Final market image (tablet)

Patient disposition by treatment sequence in Arm 1 – Subsequent cycles (Randomized set)

Disposition	All Patients N=19[†] n (%)
Ongoing	**1 (5.3)**
Discontinued	**18 (94.7)**
Primary reason for end of treatment	
Adverse event	3 (15.8)
Patient withdrew consent	1 (5.3)
Investigators decision in the patients best interest	4 (21.1)
Disease progression	10 (52.6)

[†] Includes all patients who were randomized and entered Cycle 2

Patient disposition by treatment sequence in Arm 2 - Cycle 1 (Randomized set)

	NM/LF/HF	LF/HF/NM	HF/NM/LF	LF/NM/HF	NM/HF/LF	HF/LF/NM	All patients
	N=7	N=6	N=8	N=4	N=8	N=9	N=42
Disposition	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Ongoing[†]	**3 (42.9)**	**3 (50.0)**	**6 (75.0)**	**4 (100.0)**	**4 (50.0)**	**5 (55.6)**	**25 (59.5)**
Discontinued[†]	**4 (57.1)**	**3 (50.0)**	**2 (25.0)**	**0**	**4 (50.0)**	**4 (44.4)**	**17 (40.5)**
Primary reason for end of treatment							
Adverse event	2 (28.6)	2 (33.3)	0	0	1 (12.5)	3 (33.3)	8 (19.0)
Patient withdrew consent	1 (14.3)	0	0	0	0	1 (11.1)	2 (4.8)
Death	0	0	1 (12.5)	0	1 (12.5)	0	2 (4.8)
Investigator's decision in the patients best interest	1 (14.3)	0	0	0	2 (25.0)	0	3 (7.1)
Disease progression	0	1 (16.7)	1 (12.5)	0	0	0	2 (4.8)

[†] Includes all randomized patients who are ongoing or discontinued prior to Cycle 2

LF=Low fat; HF=High fat; NM=No meal

Patient disposition by treatment sequence in Arm 2 – Subsequent cycles (Randomized set)

	All Patients N=25[†]
Disposition	**n (%)**
Ongoing	**2 (8.0)**
Discontinued	**23 (92.0)**
Primary reason for end of treatment	
Adverse event	6 (24.0)
Patient withdrew consent	1 (4.0)
Investigators decision in the patients best interest	5 (20.0)
Disease progression	11 (44.0)

[†] Includes all patients who were randomized and entered Cycle 2

Patient disposition: Final data cut-off (01-Nov-2013)

Patient disposition by treatment sequence in Arm 1 – Subsequent cycles (Randomized set)

Disposition	All Patients N=19[†] n (%)
Ongoing	**0**
Discontinued during subsequent cycles	**19 (100)**
Primary reason for end of treatment	
Adverse event	3 (15.8)
Patient withdrew consent	2 (10.5)
Investigators decision in the patients best interest	4 (21.1)
Disease progression	10 (52.6)

[†] Includes all patients who were randomized and entered Cycle 2

-At the interim CSR cutoff date of 14-Mar-2012 three patients were receiving dovitinib treatment; three patients had ended dovitinib treatment but continued in followed up.

Patient disposition by treatment sequence in Arm 2 – Subsequent cycles (Randomized set)

Disposition	All Patients N=25[†] n (%)
Ongoing	**0**
Discontinued during subsequent cycles	**25 (100)**
Primary reason for end of treatment	
Adverse event	6 (24.0)
Patient withdrew consent	1 (4.0)
Investigators decision in the patients best interest	7 (28.0)
Disease progression	11 (44.0)

[†] Includes all patients who were randomized and entered Cycle 2

-At the interim CSR cutoff date of 14-Mar-2012 three patients were receiving dovitinib treatment; three patients had ended dovitinib treatment but continued in followed up.

Baseline Characteristics

Primary data cut-off (14-Mar-2012)

Summary of demographic characteristics by treatment sequence – Arm 1 (Randomized set)

	CSF/FMI	FMI/CSF	All Patients
Demographic Variable	**N=10**	**N=11**	**N=21**
Age (years)			
n	**10**	**11**	**21**
Mean (Standard deviation)	66.0 (10.59)	56.9 (13.63)	61.2 (12.84)
Median	67.0	59.0	64.0
Min, Max	45, 79	36, 82	36, 82
Sex			
Male	6 (60.0)	5 (45.5)	11 (52.4)
Female	4 (40.0)	6 (54.5)	10 (47.6)
Race (n %)			
Caucasian	9 (90.0)	8 (72.7)	17 (81.0)
Black	0	2 (18.2)	2 (9.5)
Native American	0	1 (9.1)	1 (4.8)
Pacific Islander	1 (10.0)	0	1 (4.8)
Ethnicity (n %)			
Other	10 (100.0)	11 (100.0)	21 (100.0)
Weight (kg)			
n	**10**	**11**	**21**
Mean (Standard deviation)	88.64 (24.315)	92.95 (33.508)	90.90 (28.850)
Median	84.65	88.00	88.00
Min, Max	63.5, 136.1	51.3, 145.7	51.3, 145.7
Height (cm)			
n	**9**	**11**	**20***
Mean (Standard deviation)	174.0 (8.56)	169.5 (9.53)	171.6 (9.16)
Median	177.0	168.0	169.0
Min, Max	163, 183	157, 193	157, 193

	CSF/FMI	FMI/CSF	All Patients
Demographic Variable	**N=10**	**N=11**	**N=21**
BMI (kg/m^2)			
n	**9**	**11**	**20***
Mean (Standard deviation)	29.75 (6.263)	32.30 (11.613)	31.15 (9.444)
Median	30.42	29.37	29.89
Min, Max	23.3, 42.0	17.8, 53.5	17.8, 53.5
WHO performance status at baseline (n%)			
0	3 (30.0)	2 (18.2)	5 (23.8)
1	6 (60.0)	9 (81.8)	15 (71.4)
2	1 (10.0)	0	1 (4.8)

*Height is missing for one patient; therefore, BMI is also missing for this patient.

The baseline weight (kg) and baseline height (cm) were defined as the last non-missing assessment of weight and height before the first study drug administration.

BMI is computed using this height and weight value for each patient.

BMI (kg/m ^{2}) = weight (kg) / height (m)^2

Baseline for WHO performance status was defined as the last non-missing value before treatment in Cycle 1.

CSF=Clinical service form (capsule); FMI=Final market image (tablet); WHO=World Health Organization; BMI=Body mass index

Summary of demographic characteristics by treatment sequence – Arm 2 (Randomized set)

	NM/LF/HF	LF/HF/NM	HF/NM/LF	LF/NM/HF	NM/HF/LF	HF/LF/NM	All Patients
Demographic Variable	**N=7**	**N=6**	**N=8**	**N=4**	**N=8**	**N=9**	**N=42**
Age (years)							
n	7	6	8	4	8	9	42

Demographic Variable	NM/LF/HF N=7	LF/HF/NM N=6	HF/NM/LF N=8	LF/NM/HF N=4	NM/HF/LF N=8	HF/LF/NM N=9	All Patients N=42
Mean (SD)	56.3	60.7	61.6	59.3	65.5	60.6	60.9
	(12.74)	(11.62)	(15.00)	(11.59)	(8.18)	(8.41)	(11.04)
Median	56.0	66.5	65.0	58.0	65.5	58.0	62.5
Min, Max	36, 69	41, 70	33, 81	47, 74	53, 75	50, 79	33, 81
Sex							
Male	3 (42.9)	4 (66.7)	3 (37.5)	2 (50.0)	2 (25.0)	6 (66.7)	20 (47.6)
Female	4 (57.1)	2 (33.3)	5 (62.5)	2 (50.0)	6 (75.0)	3 (33.3)	22 (52.4)
Race (n %)							
Caucasian	5 (71.4)	5 (83.3)	8 (100.0)	3 (75.0)	6 (75.0)	9 (100.0)	36 (85.7)
Black	1 (14.3)	0	0	1 (25.0)	1 (12.5)	0	3 (7.1)
Asian	0	0	0	0	1 (12.5)	0	1 (2.4)
Other	1 (14.3)	1 (16.7)	0	0	0	0	2 (4.8)
Ethnicity (n%)							
Hispanic/ Latino	1 (14.3)	1 (16.7)	1 (12.5)	0	0	1 (11.1)	4 (9.5)
Other	5 (71.4)	5 (83.3)	7 (87.5)	4 (100.0)	8 (100.0)	8 (88.9)	37 (88.1)
Mixed ethnicity	1 (14.3)	0	0	0	0	0	1 (2.4)
Weight (kg)							
n	**7**	**6**	**8**	**4**	**8**	**9**	**42**
Mean (SD)	74.33	74.17	88.13	78.38	66.40	83.29	77.73
	(4.857)	(28.901)	(28.386)	(14.385)	(24.201)	(15.441)	(21.479)

Demographic Variable	NM/LF/HF N=7	LF/HF/NM N=6	HF/NM/LF N=8	LF/NM/HF N=4	NM/HF/LF N=8	HF/LF/NM N=9	All Patients N=42
Median	75.50	71.20	87.25	76.80	62.50	79.30	75.70
Min, Max	65.8, 81.4	40.3, 114.9	52.9, 149.4	62.6, 97.3	40.1, 110.4	59.0, 108.5	40.1,149.4
Height (cm)							
n	**7**	**6**	**8**	**4**	**8**	**8**	**41**
Mean (SD)	171.4	172.8	167.1	171.8	160.9	166.9	167.9
	(9.48)	(14.62)	(11.89)	(7.68)	(10.45)	(4.58)	(10.47)
Median	170.0	177.0	165.0	172.5	163.0	165.5	166.0
Min, Max	160, 183	152, 188	154, 188	162, 180	139, 175	161, 173	139, 188
BMI (kg/m^2)							
n	**7**	**6**	**8**	**4**	**8**	**8**	**41**
Mean (SD)	25.46	24.12	30.96	26.93	25.38	30.17	27.38
	(2.984)	(6.678)	(6.271)	(7.138)	(7.785)	(5.041)	(6.313)
Median	25.12	21.61	30.56	25.10	24.50	30.25	26.64
Min, Max	21.6, 29.6	16.1, 32.5	22.3, 42.3	20.4, 37.1	15.1, 40.6	22.8, 38.9	15.1, 42.3
WHO performance status at baseline (n%)							
0	3 (42.9)	2 (33.3)	2 (25.0)	1 (25.0)	2 (25.0)	1 (11.1)	11 (26.2)
1	4 (57.1)	4 (66.7)	6 (75.0)	3 (75.0)	6 (75.0)	7 (77.8)	30 (71.4)

Demographic Variable	NM/LF/HF N=7	LF/HF/NM N=6	HF/NM/LF N=8	LF/NM/HF N=4	NM/HF/LF N=8	HF/LF/NM N=9	All Patients N=42
2	0	0	0	0	0	1 (11.1)	1 (2.4)

The baseline weight (kg) and baseline height (cm) were defined as the last non-missing assessment of weight and height before the first study drug administration.

BMI was computed using the baseline height and weight value for each patient.

BMI (kg/m^2) = weight (kg) / height $(m)^2$

Baseline for WHO performance status was defined as the last non-missing value before treatment in Cycle 1.

LF=Low fat; HF=High fat; NM=No meal; SD=Standard deviation; BMI=Body mass index; WHO=World Health Organization

Summary of Efficacy

Primary Outcome Result(s)

Summary of dovitinib primary PK parameters in plasma by treatment – Arm 1 (PK set)

	Statistics	AUCinf** (h.ng/mL)	AUClast (h.ng/mL)	Cmax (ng/mL)	Tmax (h)
CSF	**n**	**4**	**17**	**17**	**17**
	Mean (SD)	5756.06 (1949.286)	5104.69 (1773.746)	201.06 (60.874)	-
	CV% mean	33.86	34.75	30.28	-
	Geo-mean	5505.86	4796.18	192.36	-
	CV% geo-mean	35.73	38.89	31.73	-
	Median	5628.67	4656.80	195.00	7.00
	Min - Max	3770.1 - 7996.8	2090.4 - 8257.3	107.0 - 313.0	4.0 - 8.1
FMI	**n**	**5**	**17**	**17**	**17**
	Mean (SD)	5409.88 (1659.751)	5009.37 (1932.796)	196.76 (50.676)	-
	CV% mean	30.68	38.58	25.75	-
	Geo-mean	5220.13	4700.22	190.94	-
	CV% geo-mean	30.19	37.49	25.48	-
	Median	4934.28	4264.54	188.00	7.00
	Min - Max	3678.1 - 7966.7	2561.8; 10141.3	136.0 - 308.0	3.8 - 23.5

CV%=coefficient of variation (%)=(sd/mean)*100

CV% geo-mean=sqrt (exp (variance for log transformed data)-1)*100
exp=exponential function; sqrt=square root ; CSF=Clinical service form (capsule); FMI=Final market image (tablet); SD=standard deviation; AUC= Area under the plasma concentration-time curve; Cmax= Maximum (peak) observed plasma concentration; Tmax= Time to reach maximum (peak) plasma concentration of drug ; PK=pharmacokinetics

Statistics	AUCinf** (h.ng/mL)	AUClast (h.ng/mL)	Cmax (ng/mL)	Tmax (h)

**Patients with extrapolated AUC greater than 20% were excluded from calculation of AUCinf, hence fewer patients are reported in this group.

Ratio of geometric means with (90% CI) of dovitinib primary PK parameters - Arm 1 (PK set)

				Treatment comparison		
					90% CI	
PK parameter (unit)	Treatment	n*	Adjusted Geo-mean	Comparison	Geo-mean ratio	Lower	Upper
AUCinf** (h.ng/mL)	CSF	4	5916.67				
	FMI	5	5007.92	FMI / CSF	0.85	0.44	1.62
AUClast (h.ng/mL)	CSF	17	4819.16				
	FMI	17	4670.31	FMI / CSF	0.97	0.88	1.07
Cmax (ng/mL)	CSF	17	192.33				
	FMI	17	190.72	FMI / CSF	0.99	0.91	1.08
Tmax (h)	CSF	17	7.00				
	FMI	17	7.00	FMI / CSF	0.03	-4.00	15.48

The model for log transformed PK parameters (AUC and Cmax) includes treatment, period and sequence as a fixed factor and patient-within-sequence as a random factor.

For Tmax, median is presented under "Adjusted Geo-Mean," median difference under 'Geo-mean Ratio', and Minimum and Maximum of treatment differences under "90% CI."

CI=Confidence interval; CSF=Clinical service form (capsule); FMI=Final market image (tablet); Geo=geometric; AUC= Area under the plasma concentration-time curve; Cmax= Maximum (peak) observed plasma concentration; Tmax= Time to reach maximum (peak) plasma concentration of drug; PK=pharmacokinetics

*Number of patients with non-missing values

**Patients with extrapolated AUC greater than 20% were excluded from calculation of AUCinf, hence fewer patients are reported in this group.

Summary of dovitinib primary PK parameters in plasma by treatment – Arm 2 (PK set)

Food state	Statistics	AUClast (h.ng/mL)	Cmax (ng/mL)	Tmax (h)
NM	**n**	**19**	**19**	**19**
	Mean (SD)	2877.17 (1202.220)	194.26 (84.353)	--
	CV% mean	41.78	43.42	--
	Geo-mean	2674.00	181.80	--
	CV% geo-mean	40.33	36.13	--
	Median	2639.00	163.00	4.02
	Min - Max	1320.6 - 6380.2	106.0 - 444.0	2.0 - 8.0
LF	**n**	**19**	**19**	**19**
	Mean (SD)	3015.22 (1798.829)	189.76 (122.965)	--
	CV% mean	59.66	64.80	--
	Geo-mean	2666.93	163.91	--
	CV% geo-mean	50.34	56.48	--
	Median	2586.95	159.00	6.03
	Min - Max	1245.4 - 7656.8	58.0 - 522.0	1.9 - 8.0
HF	**n**	**19**	**19**	**19**
	Mean (SD)	2681.25 (1265.863)	167.72 (86.468)	--
	CV% mean	47.21	51.56	--
	Geo-mean	2439.29	148.49	--
	CV% geo-mean	46.23	54.16	--
	Median	2439.72	147.00	6.10
	Min - Max	1097.6 - 5647.1	68.3 - 346.0	2.0 - 24.3

Food state	Statistics	AUClast (h.ng/mL)	Cmax (ng/mL)	Tmax (h)

CV%=coefficient of variation (%)=(sd/mean)*100

CV% geo-mean=sqrt (exp (variance for log transformed data)-1)*100
exp=exponential function; sqrt=square root ; SD=standard deviation; LF=Low fat; HF=High fat; NM=No meal; AUC= Area under the plasma concentration-time curve; Cmax= Maximum (peak) observed plasma concentration; Tmax= Time to reach maximum (peak) plasma concentration of drug; PK=pharmacokinetics

Ratio of geometric means with (90% CI) for dovitinib primary PK parameters – Arm 2 (PK set)

PK parameter (unit)	Food state	n*	Adjusted Geo-mean	Comparisons	Food state comparison		
					Geo-mean Ratio**	90% Confidence interval	
						Lower	Upper
AUClast (ng.h/mL)	NM	19	2701.23	--	--	--	--
	LF	19	2662.23	LF/NM	0.99	0.88	1.10
	HF	19	2464.14	HF/NM	0.91	0.81	1.02
Cmax (ng/mL)	NM	19	184.76	--			
	LF	19	166.03	LF/NM	0.90	0.78	1.03
	HF	19	150.91	HF/NM	0.82	0.71	0.94
Tmax (h)	NM	19	4.02				
	LF	19	6.03	LF/NM	0.12	-4.82	3.22
	HF	19	6.10	HF/NM	1.97	-3.72	20.25

*Number of patients with non-missing values

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 (AUC and Cmax) includes food state, period, and sequence as a fixed factor and patient within sequence as a random factor

For Tmax, median is presented under “Adjusted Geo-Mean,” median difference under ‘Geo-mean Ratio’, and Minimum and Maximum of treatment differences under “90% CI’.

CI=confidence interval; Geo-mean=geometric mean; LF=Low fat; HF=High fat; NM=No meal; AUC= Area under the plasma concentration-time curve; Cmax= Maximum (peak) observed plasma concentration; Tmax= Time to reach maximum (peak) plasma concentration of drug; PK=pharmacokinetics

Secondary Outcome Result(s)

Efficacy Results – Primary cut-off date (14-Mar-2012)

The response to treatment in Arm 1 and Arm 2 was to be assessed by the Investigator according to Novartis Guidelines for Response (Version 2, based on RECIST 1.0).

In Arm 1, of 21 patients randomized, 17 patients had at least one post-baseline tumor assessment and 4 patients discontinued before the first scheduled tumor assessment. Fourteen of 21 patients (66.7%) achieved an overall response of stable disease (SD), and 3 of 21 patients (14.3%) had progressive disease (PD). No responses of complete response (CR) or partial response (PR) were observed.

Among the 14 patients with stable disease, 7 patients had a duration on treatment of > 120 days:

- 3 patients with RCC were on treatment for 129 days, 162 days, and 213 days
- 3 patients with thyroid cancer were on treatment for 242 days, 348 days, and 590 days (note: this patient was still receiving treatment as of the CSR's data cut-off date)
- 1 patient with gastrointestinal stromal tumor (GIST) was on treatment for 145 days

In Arm 2, of 42 patients randomized, 26 patients had at least one post-baseline tumor assessment and 16 patients discontinued before the first scheduled tumor assessment. One patient of 42 (2.4%) with heavily pretreated adenocarcinoma of the endometrium had an unconfirmed PR at evaluation 1, with PD at evaluation 2. This patient died due to disease progression 10 days after the last dose of the study medication. Fifteen of 42 patients (35.7%) achieved an overall response of SD, while 10 of 42 patients (23.8%) had PD.

Among the 15 patients with stable disease, 3 patients had duration on treatment of > 120 days:

- 1 patient with bladder cancer had duration on treatment of 123 days
- 1 patient with thymoma were on treatment for 130 days
- 1 patient with RCC were on treatment for 131 days

Efficacy Results – Final cut-off date (-01-Nov-2013)

Efficacy data for the six ongoing patients after 14-Mar-2012 were as follows:

- 1 patient with clear cell, granular cell, and sarcomatoid of the kidneys had two post-baseline tumor evaluations. An overall response of stable disease was observed at each evaluation. The last study dose was administered on 26-Feb-2012 (study Day 131).
- 1 patient with adenoid cystic carcinoma of the oral cavity had three post-baseline tumor evaluations. An overall response of stable disease was observed at each evaluation. The last study dose was administered on 15-Apr-2012 (study Day 153).
- 1 patient with leydig cell carcinoma of the testis had one post-baseline tumor evaluation. An overall response of progressive disease was observed at this evaluation. The last study dose was administered on 12-Mar-2012 (study Day 50).
- 1 patient with follicular carcinoma of the thyroid had 12 post-baseline tumor evaluations. An overall response of stable disease was observed at each evaluation, except for four evaluations (Evaluations 5, 6, 10, and 12) for which overall response was unknown because the target lesion was not measured and/or the non-target lesion was not evaluated. The last study dose was administered on 16-Aug-2013 (study Day 1115).
- 1 patient with a gastrointestinal stromal tumor had nine post-baseline tumor evaluations. An overall response of stable disease was observed at each evaluation. The last study dose was administered on 29-Mar-2013 (study Day 502).
- 1 patient with adenocarcinoma of the colon had one post-baseline tumor evaluation. An overall response of stable disease was observed at this evaluation. The last study dose was administered on 18-Feb-2012 (study Day 52).

Secondary PK Results – Arm 1

Summary of dovitinib secondary PK parameters in plasma by treatment – Arm 1 (PK set)

	Statistics	T1/2* (h)	CL/F** (L/h)	Vz/F** (L)
CSF	**n**	**7**	**4**	**4**
	Mean (SD)	18.62 (3.228)	94.95 (32.304)	2346.63 (822.535)
	CV% mean	17.34	34.02	35.05
	Geo-mean	18.39	90.81	2229.04
	CV% geo-mean	17.05	35.73	39.45
	Median	18.32	92.33	2422.27
	Min - Max	15.0 - 24.3	62.5 - 132.6	1379.5 - 3162.5

FMI	n	6	5	5
	Mean (SD)	16.38 (3.350)	99.06 (27.851)	2180.17 (635.770)
	CV% mean	20.45	28.12	29.16
	Geo-mean	16.09	95.78	2106.81
	CV% geo-mean	20.70	30.19	30.04
	Median	16.09	101.33	2000.09
	Min - Max	12.4 - 21.1	62.8 - 135.9	1406.0 - 3108.7

CV%=coefficient of variation (%)=(sd/mean)*100

CV% geo-mean=sqrt (exp (variance for log transformed data)-1)*100
CSF=Clinical service form (capsule); exp=exponential function; sqrt=square root ; FMI=Final market image (tablet); SD=Standard deviation; T1/2= Elimination half-life associated with the terminal slope (z)of a semi-logarithmic concentration-time curve; CL/F= Total body clearance; Vz/F= Apparent volume of distribution during terminal phase; PK=pharmacokinetics

*If Rsq adjusted is less than 0.75, then T1/2 is not reported for these patients

**Secondary PK parameters like CL/F and Vz/F were not reported if extrapolated AUC is greater than 20%

Summary of Safety

Safety Results – Primary cut-off date (14-Mar-2012)

Adverse events, regardless of causality, by primary system organ class during Cycle 1 – Arm 1 (Safety set)

Primary system organ class	All patients N=21 n (%)
Any primary system organ class	**20 (95.2)**
Gastrointestinal disorders	13 (61.9)
Blood and lymphatic system disorders	7 (33.3)
General disorders and administration site conditions	7 (33.3)
Metabolism and nutrition disorders	7 (33.3)

Primary system organ class	All patients N=21 n (%)
Investigations	6 (28.6)
Nervous system disorders	5 (23.8)
Musculoskeletal and connective tissue disorders	4 (19.0)
Skin and subcutaneous tissue disorders	4 (19.0)
Infections and infestations	2 (9.5)
Respiratory, thoracic and mediastinal disorders	2 (9.5)
Vascular disorders	1 (4.8)

Primary system organ classes are presented in descending order of frequency.
Only AEs starting in Cycle 1 are reported here, regardless of end date.

Adverse events, irrespective of causality, by primary system organ class during Cycle 1 – Arm 2 (Safety set)

Primary system organ class	All patients N=42 n (%)
Any primary system organ class	**41 (97.6)**
Gastrointestinal disorders	35 (83.3)
General disorders and administration site conditions	25 (59.5)
Metabolism and nutrition disorders	15 (35.7)
Nervous system disorders	14 (33.3)
Musculoskeletal and connective tissue disorders	13 (31.0)
Respiratory, thoracic and mediastinal disorders	11 (26.2)
Investigations	10 (23.8)
Skin and subcutaneous tissue disorders	9 (21.4)
Psychiatric disorders	5 (11.9)
Vascular disorders	5 (11.9)
Infections and infestations	4 (9.5)

Primary system organ class	All patients N=42 n (%)
Blood and lymphatic system disorders	3 (7.1)
Cardiac disorders	3 (7.1)
Eye disorders	2 (4.8)
Injury, poisoning and procedural complications	2 (4.8)
Renal and urinary disorders	2 (4.8)
Ear and labyrinth disorders	1 (2.4)
Endocrine disorders	1 (2.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (2.4)
Reproductive system and breast disorders	1 (2.4)

Primary system organ classes are presented in descending order of frequency.
Only AEs starting in Cycle 1 are reported here, regardless of end date.

Adverse events, irrespective of causality, by primary system organ class during subsequent cycles – Arm 1 (Safety set who entered Cycle 2)

Primary system organ class	All patients N=19 n (%)
Any primary system organ class	18 (94.7)
Gastrointestinal disorders	16 (84.2)
Metabolism and nutrition disorders	14 (73.7)
General disorders & administration site conditions	13 (68.4)
Investigations	11 (57.9)
Musculoskeletal & connective tissue disorders	10 (52.6)
Nervous system disorders	9 (47.4)
Respiratory, thoracic & mediastinal disorders	8 (42.1)

Primary system organ class	All patients N=19 n (%)
Blood and lymphatic system disorders	7 (36.8)
Infections & infestations	6 (31.6)
Skin & subcutaneous tissue disorders	5 (26.3)
Injury, poisoning and procedural complications	4 (21.1)
Psychiatric disorders	4 (21.1)
Vascular disorders	4 (21.1)
Renal & urinary disorders	3 (15.8)
Cardiac disorders	2 (10.5)
Eye disorders	2 (10.5)
Endocrine disorders	1 (5.3)
Reproductive system and breast disorders	1 (5.3)

Primary system organ classes are presented in descending order of frequency.
Only AEs starting in Cycle 2 and later or AEs of Cycle 1 worsening in a subsequent cycle are reported here.

Adverse events, irrespective of causality, by primary system organ class during subsequent cycles – Arm 2 (Safety set who entered Cycle 2)

Primary system organ class	All patients N=25 n (%)
Any primary system organ class	**25 (100.0)**
Gastrointestinal disorders	21 (84.0)
General disorders & administration site conditions	14 (56.0)
Musculoskeletal & connective tissue disorders	12 (48.0)
Respiratory, thoracic & mediastinal disorders	12 (48.0)
Skin & subcutaneous tissue disorders	10 (40.0)

Primary system organ class	All patients N=25 n (%)
Metabolism and nutrition disorders	9 (36.0)
Investigations	8 (32.0)
Nervous system disorders	8 (32.0)
Blood and lymphatic system disorders	6 (24.0)
Infections & infestations	6 (24.0)
Vascular disorders	6 (24.0)
Psychiatric disorders	5 (20.0)
Cardiac disorders	4 (16.0)
Eye disorders	3 (12.0)
Injury, poisoning and procedural complications	2 (8.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (8.0)
Ear and labyrinth disorders	1 (4.0)
Renal & urinary disorders	1 (4.0)
Reproductive system and breast disorders	1 (4.0)

Primary system organ classes are presented in descending order of frequency.
Only AEs starting in Cycle 2 and later or AEs of Cycle 1 worsening in a subsequent cycle are reported here.

Adverse events (occurring with at least 10% incidence for all grades) irrespective of causality by preferred term and maximum grade during Cycle 1 – Arm 1 (Safety set)

Primary System Organ Class Preferred Term*	All Patients N=21 n (%)
-Any AE	
-Total	20 (95.2)
Grade 1	6 (28.6)

Primary System Organ Class Preferred Term*	All Patients N=21 n (%)
Grade 2	10 (47.6)
Grade 3	4 (19.0)
Grade 4	0
Nausea	
Grade 1	7 (33.3)
Grade 2	1 (4.8)
Grade 3	0
Grade 4	0
Diarrhoea	
Grade 1	3 (14.3)
Grade 2	2 (9.5)
Grade 3	1 (4.8)
Grade 4	0
Vomiting	
Grade 1	3 (14.3)
Grade 2	2 (9.5)
Grade 3	1 (4.8)
Grade 4	0
Anaemia	
Grade 1	1 (4.8)
Grade 2	4 (19.0)
Grade 3	0
Grade 4	0

Primary System Organ Class Preferred Term*	All Patients N=21 n (%)
Hypertriglyceridaemia	
Grade 1	3 (14.3)
Grade 2	1 (4.8)
Grade 3	0
Grade 4	0
Lymphopenia	
Grade 1	0 (0.0)
Grade 2	3 (14.3)
Grade 3	1 (4.8)
Grade 4	0
Dizziness	
Grade 1	3 (14.3)
Grade 2	0
Grade 3	0
Grade 4	0
Fatigue	
Grade 1	2 (9.5)
Grade 2	1 (4.8)
Grade 3	0
Grade 4	0
Pyrexia	
Grade 1	3 (14.3)
Grade 2	0
Grade 3	0

Primary System Organ Class Preferred Term*	All Patients N=21 n (%)
Grade 4	0
Blood alkaline phosphatase increased	
Grade 1	1 (4.8)
Grade 2	1 (4.8)
Grade 3	1 (4.8)
Grade 4	0

*A patient with multiple grade ratings for an AE while on a treatment is only counted under the maximum rating.
Only AEs starting in Cycle 1 are reported here, regardless of end date.

Adverse events (occurring with at least 10% incidence for all grades) irrespective of causality, by preferred term and maximum grade during Cycle 1 – Arm 2 (Safety set)

Primary System Organ Class Preferred Term*	All Patients N=42 n (%)
-Any primary system organ class	
-Total	41 (97.6)
Grade 1	11 (26.2)
Grade 2	11 (26.2)
Grade 3	16 (38.1)
Grade 4	3 (7.1)
Nausea	
Grade 1	20 (47.6)
Grade 2	4 (9.5)
Grade 3	1 (2.4)
Grade 4	0

Primary System Organ Class Preferred Term*	All Patients N=42 n (%)
Diarrhoea	
Grade 1	15 (35.7)
Grade 2	4 (9.5)
Grade 3	0
Grade 4	0
Vomiting	
Grade 1	13 (31.0)
Grade 2	1 (2.4)
Grade 3	2 (4.8)
Grade 4	0
Fatigue	
Grade 1	6 (14.3)
Grade 2	5 (11.9)
Grade 3	4 (9.5)
Grade 4	0
Decreased appetite	
Grade 1	6 (14.3)
Grade 2	3 (7.1)
Grade 3	1 (2.4)
Grade 4	0
Constipation	
Grade 1	4 (9.5)
Grade 2	3 (7.1)

Primary System Organ Class Preferred Term*	All Patients N=42 n (%)
Grade 3	0
Grade 4	0
Dehydration	
Grade 1	2 (4.8)
Grade 2	5 (11.9)
Grade 3	0
Grade 4	0
Back pain	
Grade 1	4 (9.5)
Grade 2	1 (2.4)
Grade 3	0
Grade 4	0
Abdominal pain	
Grade 1	3 (7.1)
Grade 2	0
Grade 3	2 (4.8)
Grade 4	0

*A patient with multiple grade ratings for an AE is only counted under the maximum rating.
Only AEs starting in Cycle 1 are reported here, regardless of end date.

Adverse events (occurring with at least 10% incidence for all grades) irrespective of causality, preferred term, and maximum grade during subsequent treatment cycles – Arm 1 (Safety set who entered Cycle 2)

Primary System Organ Class Preferred Term*	All Patients, N=19 n (%)
-Any primary system organ class	
-Total	18 (94.7)
Grade 1	1 (5.3)
Grade 2	2 (10.5)
Grade 3	14 (73.7)
Grade 4	1 (5.3)
Vomiting	
Grade 1	11 (57.9)
Grade 2	1 (5.3)
Grade 3	1 (5.3)
Grade 4	0
Diarrhoea	
Grade 1	8 (42.1)
Grade 2	2 (10.5)
Grade 3	1 (5.3)
Grade 4	0
Fatigue	
Grade 1	1 (5.3)
Grade 2	7 (36.8)
Grade 3	1 (5.3)
Grade 4	0

Primary System Organ Class Preferred Term*	All Patients, N=19 n (%)
Hypertriglyceridaemia	
Grade 1	3 (15.8)
Grade 2	1 (5.3)
Grade 3	4 (21.1)
Grade 4	0
Nausea	
Grade 1	7 (36.8)
Grade 2	0
Grade 3	1 (5.3)
Grade 4	0
Blood alkaline phosphatase increased	
Grade 1	4 (21.1)
Grade 2	3 (15.8)
Grade 3	1 (5.3)
Grade 4	0
Anaemia	
Grade 1	2 (10.5)
Grade 2	4 (21.1)
Grade 3	0
Grade 4	0
Hypoalbuminaemia	
Grade 1	3 (15.8)
Grade 2	3 (15.8)

Primary System Organ Class Preferred Term*	All Patients, N=19 n (%)
Grade 3	0
Grade 4	0
Decreased appetite	
Grade 1	4 (21.1)
Grade 2	1 (5.3)
Grade 3	0
Grade 4	0
Dyspnoea	
Grade 1	3 (15.8)
Grade 2	1 (5.3)
Grade 3	1 (5.3)
Grade 4	0
Hyponatraemia	
Grade 1	3 (15.8)
Grade 2	0
Grade 3	2 (10.5)
Grade 4	0
Asthenia	
Grade 1	3 (15.8)
Grade 2	1 (5.3)
Grade 3	0
Grade 4	0
Back pain	

Primary System Organ Class Preferred Term*	All Patients, N=19 n (%)
Grade 1	2 (10.5)
Grade 2	2 (10.5)
Grade 3	0
Grade 4	0
Fall	
Grade 1	3 (15.8)
Grade 2	0 (0.0)
Grade 3	1 (5.3)
Grade 4	0
Gamma-glutamyltransferase increased	
Grade 1	2 (10.5)
Grade 2	2 (10.5)
Grade 3	0
Grade 4	0
Oedema peripheral	
Grade 1	2 (10.5)
Grade 2	1 (5.3)
Grade 3	1 (5.3)
Grade 4	0
Pain in extremity	
Grade 1	3 (15.8)
Grade 2	1 (5.3)
Grade 3	0
Grade 4	0

Primary System Organ Class Preferred Term*	All Patients, N=19 n (%)
Rash	
Grade 1	4 (21.1)
Grade 2	0
Grade 3	0
Grade 4	0
Pneumonia	
Grade 1	0
Grade 2	0
Grade 3	3 (15.8)
Grade 4	0
Blood creatinine increased	
Grade 1	3 (15.8)
Grade 2	0
Grade 3	0
Grade 4	0
Confusional state	
Grade 1	3 (15.8)
Grade 2	0
Grade 3	0
Grade 4	0
Deep vein thrombosis	
Grade 1	0
Grade 2	3 (15.8)

Primary System Organ Class Preferred Term*	All Patients, N=19 n (%)
Grade 3	0
Grade 4	0
Dehydration	
Grade 1	2 (10.5)
Grade 2	0
Grade 3	1 (5.3)
Grade 4	0
Headache	
Grade 1	3 (15.8)
Grade 2	0
Grade 3	0
Grade 4	0
Hypocalcaemia	
Grade 1	2 (10.5)
Grade 2	0
Grade 3	1 (5.3)
Grade 4	0
Lymphopenia	
Grade 1	0
Grade 2	2 (10.5)
Grade 3	1 (5.3)
Grade 4	0
Muscular weakness	

Primary System Organ Class Preferred Term*	All Patients, N=19 n (%)
Grade 1	1 (5.3)
Grade 2	1 (5.3)
Grade 3	1 (5.3)
Grade 4	0
Aspartate aminotransferase increased	
Grade 1	2 (10.5)
Grade 2	0
Grade 3	0
Grade 4	0
Dysphonia	
Grade 1	2 (10.5)
Grade 2	0
Grade 3	0
Grade 4	0
Hypokalaemia	
Grade 1	1 (5.3)
Grade 2	0 (0.0)
Grade 3	1 (5.3)
Grade 4	0
Lipase increased	
Grade 1	1 (5.3)
Grade 2	0 (0.0)
Grade 3	1 (5.3)
Grade 4	0

Primary System Organ Class Preferred Term*	All Patients, N=19 n (%)
Oropharyngeal pain	
Grade 1	2 (10.5)
Grade 2	0
Grade 3	0
Grade 4	0
Pain	
Grade 1	1 (5.3)
Grade 2	1 (5.3)
Grade 3	0
Grade 4	0
Platelet count decreased	
Grade 1	1 (5.3)
Grade 2	1 (5.3)
Grade 3	0
Grade 4	0
White blood cell count decreased	
Grade 1	0
Grade 2	2 (10.5)
Grade 3	0
Grade 4	0

*A patient with multiple grade ratings for an AE while on treatment is only counted under the maximum rating.

Only AEs starting in Cycle 2 and later or AEs of Cycle 1 worsening in a subsequent cycle are reported here.

Adverse events (occurring with at least 10% incidence for all grades) irrespective of causality, by primary system organ class, preferred term, and maximum grade during subsequent treatment cycles – Arm 2 (Safety set who entered Cycle 2)

Primary System Organ Class Preferred Term*	All Patients N=25 n (%)
-Any AE	
-Total	25 (100.0)
Grade 1	1 (4.0)
Grade 2	4 (16.0)
Grade 3	16 (64.0)
Grade 4	4 (16.0)
Nausea	
Grade 1	5 (20.0)
Grade 2	6 (24.0)
Grade 3	1 (4.0)
Grade 4	0
Vomiting	
Grade 1	7 (28.0)
Grade 2	3 (12.0)
Grade 3	1 (4.0)
Grade 4	0
Diarrhoea	
Grade 1	7 (28.0)
Grade 2	3 (12.0)
Grade 3	0
Grade 4	0
Fatigue	

Primary System Organ Class Preferred Term*	All Patients N=25 n (%)
Grade 1	1 (4.0)
Grade 2	4 (16.0)
Grade 3	5 (20.0)
Grade 4	0
Constipation	
Grade 1	3 (12.0)
Grade 2	3 (12.0)
Grade 3	0
Grade 4	0
Dyspnoea	
Grade 1	4 (16.0)
Grade 2	2 (8.0)
Grade 3	0
Grade 4	0
Anaemia	
Grade 1	1 (4.0)
Grade 2	3 (12.0)
Grade 3	0
Grade 4	0
Blood alkaline phosphatase increased	
Grade 1	0
Grade 2	2 (8.0)
Grade 3	2 (8.0)
Grade 4	0

Primary System Organ Class Preferred Term*	All Patients N=25 n (%)
Decreased appetite	
Grade 1	2 (8.0)
Grade 2	2 (8.0)
Grade 3	0
Grade 4	0
Dehydration	
Grade 1	1 (4.0)
Grade 2	1 (4.0)
Grade 3	2 (8.0)
Grade 4	0
Dermatitis acneiform	
Grade 1	3 (12.0)
Grade 2	0
Grade 3	1 (4.0)
Grade 4	0
Hypotension	
Grade 1	1 (4.0)
Grade 2	2 (8.0)
Grade 3	1 (4.0)
Grade 4	0
Abdominal pain	
Grade 1	2 (8.0)
Grade 2	0

Primary System Organ Class Preferred Term*	All Patients N=25 n (%)
Grade 3	1 (4.0)
Grade 4	0
Abdominal pain upper	
Grade 1	2 (8.0)
Grade 2	0
Grade 3	1 (4.0)
Grade 4	0
Asthenia	
Grade 1	0 (0.0)
Grade 2	1 (4.0)
Grade 3	2 (8.0)
Grade 4	0
Back pain	
Grade 1	1 (4.0)
Grade 2	1 (4.0)
Grade 3	1 (4.0)
Grade 4	0
Confusional state	
Grade 1	2 (8.0)
Grade 2	1 (4.0)
Grade 3	0
Grade 4	0
Dizziness	

Primary System Organ Class Preferred Term*	All Patients N=25 n (%)
Grade 1	3 (12.0)
Grade 2	0
Grade 3	0
Grade 4	0
Pain in extremity	
Grade 1	2 (8.0)
Grade 2	1 (4.0)
Grade 3	0
Grade 4	0
Weight decreased	
Grade 1	1 (4.0)
Grade 2	1 (4.0)
Grade 3	1 (4.0)
Grade 4	0

*A patient with multiple grade ratings for an AE is only counted under the maximum rating.
Only AEs starting in Cycle 2 and later or AEs of Cycle 1 worsening in a subsequent cycle are reported here.

Serious Adverse Events and Deaths

Summary of patients with at least one adverse event in any category during Cycle 1– Arm 1 (Safety set)

Overview of adverse events	All patients N=21 n (%)
Adverse events (AEs)	**20 (95.2)**
Grade 3-4 AEs	4 (19.0)
Suspected to be drug-related	2 (9.5)
All deaths	**0**
AEs suspected to be drug-related	**18 (85.7)**
Serious adverse events (SAEs)	**2 (9.5)**
AEs leading to discontinuation	**1 (4.8)**
AEs requiring dose adjustment or interruption	**1 (4.8)**

A patient with multiple grade ratings for an AE while on a treatment is only counted under the maximum rating.

Treatment-emergent AEs starting in Cycle 1 and on-treatment deaths (first dose date to last dose date + 28 days) in Cycle 1 are reported here, regardless of end date.

Summary of patients with at least one adverse event in any category during subsequent cycles – Arm 1 (Safety set who entered Cycle 2)

Overview of adverse events	All patients N=19 n (%)
Adverse events (AEs)	**18 (94.7)**
Grade 3-4 AEs	15 (78.9)
Suspected to be drug-related	9 (47.4)
All deaths	**0**
AEs suspected to be drug-related	**18 (94.7)**
Serious adverse events (SAEs)	**9 (47.4)**
AEs leading to discontinuation	**3 (15.8)**
AEs requiring dose adjustment or interruption	**13 (68.4)**

A patient with multiple grade ratings for an AE while on a treatment is only counted under the maximum rating.

Only treatment-emergent AEs (and on-treatment deaths (first dose date to last dose date + 28 days)) starting in Cycle 2 and later or AEs of Cycle 1 worsening in a subsequent cycle are reported here.

Summary of patients with at least one adverse event in any category during Cycle 1 -– Arm 2 (Safety set)

Overview of adverse events	All patients N=42 n (%)
Adverse events (AEs)	**41 (97.6)**
Grade 3-4 AEs	19 (45.2)
Suspected to be drug-related	13 (31.0)
All deaths	**2 (4.8)**
AEs suspected to be drug-related	**41 (97.6)**
Serious adverse events (SAEs)	**6 (14.3)**
AEs leading to discontinuation	**9 (21.4)**

Overview of adverse events	All patients N=42 n (%)
AEs requiring dose adjustment or interruption	**9 (21.4)**

A patient with multiple grade ratings for an AE while on a treatment is only counted under the maximum rating.

Only treatment-emergent AEs starting in Cycle 1 and on-treatment deaths (first dose date to last dose date + 28 days) in Cycle 1 are reported here, regardless of end date.

Summary of patients with at least one adverse event in any category during subsequent cycles -– Arm 2 (Safety set who entered Cycle 2)

Overview of adverse events	All patients N=25 n (%)
Adverse events (AEs)	**25 (100.0)**
Grade 3-4 AEs	20 (80.0)
Suspected to be drug-related	14 (56.0)
All deaths (on treatment)*	**5 (20.0)**
AEs suspected to be drug-related	**25 (100.0)**
Serious adverse events (SAEs)	**11 (44.0)**
AEs leading to discontinuation	**6 (24.0)**
AEs requiring dose adjustment or interruption	**13 (52.0)**

*On treatment refers to any event that occurred between the first dose through 28 days after the last dose.

A patient with multiple grade ratings for an AE while on a treatment is only counted under the maximum rating.

Only treatment-emergent AEs (and on-treatment deaths (first dose date to last dose date + 28 days) starting in Cycle 2 and later or AEs of Cycle 1 worsening in a subsequent cycle are reported here.

Safety Results – Final cut-off date (01-Nov-2013)

Patient with clear cell, granular cell, and sarcomatoid of the kidneys had no new grade 1, 2, or 3 AEs and one new grade 4 SAE of myocardial infarction (not suspected) since the data cut-off date of 14-Mar-2012.

AEs that started before 14-Mar-2012 included 18 grade 1 AEs: vomiting (5 instances, all suspected), hyperhidrosis (suspected), upper abdominal pain (suspected), arthropod bite (not suspected), hypotension (not suspected), rhinitis (not suspected), dyspnea (not suspected), respiratory tract irritation (not suspected), dizziness (suspected), chills (suspected), fall (not suspected), chest pain (not suspected), pleural effusion (not suspected), hypercholesterolemia (not suspected)); one grade 2 AE (thrombophlebitis (not suspected)); and two grade 3 AEs (hypotension (not suspected) and dehydration (suspected)).

Patient with adenoid cystic carcinoma of the oral cavity had no new grade 2, 3, or 4 AEs since the data cut-off date of 14-Mar-2012. Newly reported grade 1 AEs after 14-Mar-2012 were: dermatitis atopic (suspected), anxiety (not suspected), myalgia (not suspected), dermatitis acneiform (suspected), pyrexia (not suspected), arthropod bite (not suspected), and rash (not suspected).

AEs that started before 14-Mar-2012 included 17 grade 1 AEs: 3 instances of nausea (both suspected), dizziness (suspected), vomiting (suspected), feeling cold (suspected), confusional state (not suspected), neck pain (not suspected), constipation (suspected), thermal burn (not suspected), diarrhea (suspected), chills (suspected), dyspepsia (suspected), pyrexia (not suspected), ear pain (not suspected), irritability (not suspected), dermatitis acneiform (suspected). Additionally, four grade 2 AEs (dyspnea (suspected), 2 instances of fatigue (one suspected and one not suspected), and cough (not suspected)) and one grade 3 AE of fatigue (suspected) were reported before the cut-off date.

Patient with leydig cell carcinoma of the testis had no new grade 2, 3, or 4 AEs since the data cut-off date of 14-Mar-2012. One grade 1 AE of burning sensation (not suspected) was newly reported after 14-Mar-2012.

AEs that started before 14-Mar-2012 included 14 grade 1 AEs: four instances of diarrhea (all suspected), hypertension (suspected), dyspnea (not suspected), bradycardia (not suspected), rash (suspected), dry throat (suspected), asthenia (suspected), hyperhidrosis (suspected), dry skin (not suspected), pruritus (not suspected), and nausea (not suspected). Additionally, one grade 2 AE of muscle spasms (suspected) was reported before the data cut-off date.

Patient with follicular carcinoma of the thyroid had no new grade 3 or 4 AEs since the data cut-off date of 14-Mar-2012. Newly reported grade 1 AEs after 14-Mar-2012 were: decreased thyroxine free (suspected), decreased tri-iodothyronine (suspected), increased blood thyroid stimulating hormone (suspected), and ecchymosis (not suspected). Newly reported grade 2 AEs included: increased blood creatinine (not suspected), 5 instances of anemia (not suspected), and wound (not suspected).

AEs that started before 14-Mar-2012 included 24 grade 1 AEs: fall (not suspected), diarrhea (suspected), arthralgia (not suspected), fatigue (suspected), edema (not suspected), confusional state (not suspected), pyrexia (suspected), gastroesophageal reflux disease (suspected), increased blood thyroid stimulating hormone (suspected), decreased tri-iodothyronine (suspected), two instances of increased thyroxine free (both suspected), asthenia (suspected), temperature intolerance (not suspected), decreased appetite (suspected), dry skin (suspected), two instances of rash (both suspected), musculoskeletal discomfort (not suspected), musculoskeletal stiffness (not suspected), urinary incontinence (not suspected), decreased appetite (suspected), prostatomegaly (not suspected), and urinary hesitation (not suspected). Additionally, 12 grade 2 AEs were reported before the data cut-off date including: hyperkalemia (not suspected), three instances of neutropenia (all suspected), two instances of decreased weight (both not suspected), two instances of decreased appetite (suspected), and four instances of anemia (one suspected and two not suspected). Grade 3 AEs occurring before the data cut-off date included: two instances of neutropenia (suspected), two instances of decreased weight (not suspected), and decreased neutrophil count (suspected).

Patient with a gastrointestinal stromal tumor had no new grade 2, 3, or 4 AEs since the data cut-off date of 14-Mar-2012. Newly reported grade 1 AEs after 14-Mar-2012 included: exertional dyspnea (not suspected), diarrhea (suspected), fatigue (suspected), sinus congestion (not suspected), abdominal distension (not suspected), and pyrexia (suspected).

AEs that started before 14-Mar-2012 included 10 grade 1 AEs: diarrhea (suspected), three incidences of headache (two not suspected and one suspected), oropharyngeal pain (not suspected), cough (not suspected), dysphonia (not suspected), increased blood cholesterol (not suspected), lower abdominal pain (not suspected), and dermatitis acneiform (suspected). Additionally, two grade 2 AEs (hypothyroidism (suspected) and weight decreased (not suspected)) and one grade 3 AE (hypertension (not suspected)) were reported before the data cut-off date.

Patient with adenocarcinoma of the colon had no new grade 2, 3, or 4 AEs since the data cut-off date of 14-Mar-2012. One grade 1 AE of cough (not suspected) was newly reported after 14-Mar-2012.

AEs that started before 14-Mar-2012 included 8 grade 1 AEs: musculoskeletal pain (not suspected), decreased appetite (suspected), fatigue (suspected), pruritus (not suspected), early satiety (not suspected), skin fissures (suspected), hypertension (suspected), and pain in extremity (not suspected). Additionally, seven grade 2 AEs (decreased appetite (suspected), hypertension (suspected), confusional state (suspected; SAE), fatigue (suspected), hypoxia (not suspected), tachycardia (not suspected), and hypotension (not suspected)) and two grade 3 AEs (asthenia (suspected; SAE) and dehydration (suspected; SAE)) were reported before the data cut-off date.

Serious Adverse Events and Deaths

Six patients were continuing in the study past the data cut-off date of 14-Mar-2012 for the initial clinical study report; of these six, three patients were still receiving treatment with dovitinib, and three patients had ended treatment with dovitinib but were still being followed up for safety, tumor assessment, and study evaluation completion assessments. The three patients received treatment for 1 month, 17 months and 12.5 months after the data cut-off date, respectively.

During this period and during the 28-day follow-up, none of these six patients died. One patient had one new grade 4 SAE of myocardial infarction since the data cut-off date.

No other SAEs were reported among the six patients since the 14-Mar-2012 data cut-off date or during the 28-day follow-up period. No other significant AEs were reported among the six patients since the data cut-off date or during the 28-day follow-up period.

One patient had SAEs of grade 3 asthenia, grade 2 confusional state, and grade 3 dehydration prior to the data cut-off date. One patient had other clinically significant events of grade 2 fatigue worsening to grade 3 fatigue (both suspected), which led to interruption of study drug and reduced dose, and one patient had one other significant event of grade 3 hypertension (not suspected) prior to the data cut-off date of 14-Mar-2012.

Other Relevant Findings

None

Conclusions:

Primary cut-off date (14-Mar-2012)

1. The bioavailability of dovitinib was similar between the CSF capsule and FMI tablet formulation.
2. Food (HF and LF) showed no effect on the systemic exposure of dovitinib and a minimal decrease in Cmax after administration as an FMI tablet. Hence, dovitinib can be taken with or without food.
3. No new safety concerns have emerged in the conduct of this trial. Dovitinib was generally safe and tolerated, and observations were consistent with previously reported data with dovitinib.
4. Most AEs continue to be of grade 1 (mild) or grade 2 (moderate) intensity.

Final cut-off date (01-Nov-2013)

- No new safety concerns were found among the six ongoing patients reported after the 14-Mar-2012 compared to results prior to the cut-off date.
- The majority of AEs reported after the data cut-off date were grade 1.
- Dovitinib was generally safe and tolerated at the 500-mg dose level on a 5 days on/2 days off schedule.
- Efficacy was limited for the six ongoing patients and did not alter the conclusion from the primary results of the initial report.

Date of Clinical Trial Report

Interim Report Date: 16-Aug-2013

Final Report Date (Published): 28-Jul-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

27-Oct-2014

Date of Latest Update

Reason for Update