Sponsor

Novartis

Generic Drug Name

dovitinib

Therapeutic Area of Trial

Advanced solid tumors

Approved Indication

Investigational

Protocol Number

CTKI258A2112

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 capsule), and the effect of food on the bioavailability of TKI258, in patients with advanced solid tumors

Study Phase

Phase I

Study Start/End Dates

25-Feb-2010 to 28-Jun-2012

Study Design/Methodology

This trial was a Phase 1, two-arm, open-label, randomized, multi-center, crossover trial to compare the relative bioavailability of the clinical service form (CSF) capsule and final market image (FMI) capsule 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 or FMI capsule formulation, followed by 7 days of rest, and then a single 500 mg dose of the other formulation. In Arm 2, Cycle 1, the effect of food on dovitinib, administered as the preferred formulation from Arm 1 (FMI capsule), was assessed under 3 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

Four study centers in the United States of America

Publication

None

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 as either a CSF (anhydrate) formulation or as a (FMI) (monohydrate) formulation. Patients were to take an oral daily dose of dovitinib at approximately the same time each day. However, on days of pharmacokinetic (PK) sampling, patients brought their dose of dovitinib to the investigative site where administration of dovitinib was 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 semilogarithmic view. All concentration data were listed using the randomized set. A formal statistical analysis was performed to estimate the relative bioavailability of dovitinib (FMI capsule formulation) compared with the CSF capsule formulation. A linear mixed-effects model was fitted to the log-transformed PK parameters, Area under the plasma concentration-time curve from time zero to the last measureable sampling time (AUClast), Area under the plasma concentration-time curve from time zero infinity (AUCinf), and maximum (peak) observed plasma concentration (Cmax) for Arm 1; and AUClast and Cmax for Arm 2). Included in the model were treatment, period, and sequence as fixed factors and subjects nested within sequences as a random factor.

For the bioavailability analysis (Arm 1), the FMI capsule formulation was the test and the intact CSF capsule formulation was the reference. For the food effect analysis (Arm 2), low Fat (LF) and high Fat (HF) food states were the test treatments and no Meal (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% CI 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 time to reach maximum (peak) plasma concentration of drug (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. The response to treatment in Arm 1 and Arm 2 was assessed by the Investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) patient lesion response.

All adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 15.0). 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: Inclusion/Exclusion Criteria and Demographics

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 10^9/L
  - Platelets ≥ 75 x 10^9/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 primary central nervous system tumors or known symptomatic cerebral metastases requiring treatment (e.g., steroids, anti-seizure medications) ≤ 3 months

prior to starting study drug

- 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 have significantly altered the absorption of dovitinib
  - Cirrhosis, chronic active hepatitis or chronic persistent hepatitis.
  - Acute or chronic renal disease

Participant Flow

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

Disposition	CSF/FMI N=11 n (%)	FMI/CSF N=12 n (%)	All patients N=23 n (%)
Ongoing[†]	10 (90.9)	10 (83.3)	20 (87.0)
Discontinued[†]	1 (9.1)	2 (16.7)	3 (13.0)
Primary reason for end of treatment			
Adverse event	1 (9.1)	2 (16.7)	3 (13.0)
Primary reason for study evaluation completion	1 (9.1)	2 (16.7)	3 (13.0)
Patient withdrew consent	0	1 (8.3)	1 (4.3)
Lost to follow-up	1 (9.1)	0	1 (4.3)
Death	0	1 (8.3)	1 (4.3)

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

CSF=clinical service form; FMI=final market image

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

Disposition	All patients N[†]=20 n (%)
Ongoing	**0**
Discontinued during subsequent cycles	**20 (100)**
Primary reason for end of treatment	
Adverse event	5 (25.0)
Patient withdrew consent	3 (15.0)
Investigators decision in the patients best interest	2 (10.0)
Disease progression	10 (50.0)
Primary reason for study evaluation completion	**19 (95.0)**
Patient withdrew consent	4 (20.0)
Lost to follow-up	3 (15.0)
Death	2 (10.0)
New cancer therapy	2 (10.0)
Disease progression	1 (5.0)

Follow up phase completed as per protocol	7 (35.0)

† Includes all patients who were randomized and entered Cycle 2

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

Disposition	NM/LF/HF N=6 n (%)	LF/HF/NM N=4 n (%)	HF/NM/LF N=5 n (%)	LF/NM/HF N=8 n (%)	NM/HF/LF N=6 n (%)	HF/LF/NM N=8 n (%)	All patients N=37 n (%)
Ongoing†	**5 (83.3)**	**4 (100)**	**3 (60.0)**	**7 (87.5)**	**3 (50.0)**	**5 (62.5)**	**27 (73.0)**
Discontinued†	**1 (16.7)**	**0**	**2 (40.0)**	**1 (12.5)**	**3 (50.0)**	**3 (37.5)**	**10 (27.0)**
Primary reason for end of treatment							
Adverse event	1 (16.7)	0	1 (20.0)	0	2 (33.3)	2 (25.0)	6 (16.2)
Investigator's decision in the patients best interest	0	0	0	0	1 (16.7)	0	1 (2.7)
Disease progression	0	0	1 (20.0)	1 (12.5)	0	1 (12.5)	3 (8.1)
Primary reason for study evaluation completion	**1 (16.7)**	**0**	**2 (40.0)**	**1 (12.5)**	**3 (50.0)**	**3 (37.5)**	**10 (27.0)**
Lost to follow-up	0	0	0	1 (12.5)	1 (16.7)	1 (12.5)	3 (8.1)
Death	0	0	1 (20.0)	0	1 (16.7)	1 (12.5)	3 (8.1)
Follow up phase completed as per protocol	1 (16.7)	0	1 (20.0)	0	1 (16.7)	1 (12.5)	4 (10.8)

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

HF=high fat; LF=low fat; NM=no meal

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

Disposition	All patients N†=27 n (%)
Ongoing	**0**
Discontinued	**27 (100)**
Primary reason for end of treatment	
Adverse event	5 (18.5)
Patient withdrew consent	1 (3.7)
Investigators decision in the patients best interest	3 (11.1)
Disease progression	18 (66.7)
Primary reason for study evaluation completion	**26 (96.3)**
Lost to follow-up	7 (25.9)

New cancer therapy	4 (14.8)
Disease progression	2 (7.4)
Follow up phase completed as per protocol	13 (48.1)

† Includes all patients who were randomized and entered Cycle 2

Baseline Characteristics

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

Demographic Variable	CSF/FMI N=11	FMI/CSF N=12	All patients N=23
Age (years)			
n	**11**	**12**	**23**
Mean (SD)	71.9 (7.49)	63.2 (9.93)	67.3 (9.74)
Median	71.0	61.0	70.0
Min, Max	58, 85	52, 79	52, 85
Sex			
Male	7 (63.6)	10 (83.3)	17 (73.9)
Female	4 (36.4)	2 (16.7)	6 (26.1)
Race (n %)			
Caucasian	10 (90.9)	10 (83.3)	20 (87.0)
Black	0	1 (8.3)	1 (4.3)
Asian	1 (9.1)	0	1 (4.3)
Native American	0	1 (8.3)	1 (4.3)
Ethnicity (n %)			
Other	11 (100)	12 (100)	23 (100)
Weight (kg)			
n	**11**	**12**	**23**
Mean (SD)	84.77 (17.999)	92.80 (21.137)	88.96 (19.684)
Median	83.40	88.80	87.10
Min, Max	63.9, 112.9	69.8, 146.6	63.9, 146.6
Height (cm)			
n	**11**	**12**	**23**
Mean (SD)	170.2 (10.88)	174.8 (9.72)	172.6 (10.32)
Median	167.0	176.5	172.0
Min, Max	152, 188	151, 188	151, 188
BMI (kg/m^2)			
n	**11**	**12**	**23**
Mean (SD)	29.38 (6.269)	30.59 (7.233)	30.01 (6.664)
Median	30.16	28.84	29.53
Min, Max	20.5, 40.5	21.1, 45.2	20.5, 45.2
WHO performance status at baseline (n %)			
0	1 (9.1)	2 (16.7)	3 (13.0)
1	10 (90.9)	9 (75.0)	19 (82.6)
2	0	1 (8.3)	1 (4.3)

BMI=body mass index; CSF=clinical service form; FMI=final market image; SD=standard deviation; WHO=World Health Organization;

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.

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=6**	**N=4**	**N=5**	**N=8**	**N=6**	**N=8**	**N=37**
Age (years)							
n	**6**	**4**	**5**	**8**	**6**	**8**	**37**
Mean (SD)	64.2 (15.38)	49.3 (10.90)	61.6 (7.89)	53.3 (11.18)	58.2 (12.88)	62.1 (9.31)	58.4 (11.80)
Median	63.5	50.5	60.0	51.0	54.0	62.0	58.0
Min, Max	47, 91	35, 61	55, 74	40, 72	44, 77	45, 74	35, 91
Sex							
Male	4 (66.7)	1 (25.0)	3 (60.0)	5 (62.5)	3 (50.0)	5 (62.5)	21 (56.8)
Female	2 (33.3)	3 (75.0)	2 (40.0)	3 (37.5)	3 (50.0)	3 (37.5)	16 (43.2)
Race (n %)							
Caucasian	5 (83.3)	4 (100)	5 (100.0)	5 (62.5)	5 (83.3)	8 (100)	32 (86.5)
Asian	1 (16.7)	0	0	1 (12.5)	1 (16.7)	0	3 (8.1)
Other	0	0	0	2 (25.0)	0	0	2 (5.4)
Ethnicity (n %)							
Hispanic/ Latino	1 (16.7)	1 (25.0)	1 (20.0)	2 (25.0)	1 (16.7)	3 (37.5)	9 (24.3)
Chinese	0	0	0	0	1 (16.7)	0	1 (2.7)
Other	5 (83.3)	3 (75.0)	4 (80.0)	6 (75.0)	4 (66.7)	5 (62.5)	27 (73.0)
Weight (kg)							
n	**5**	**4**	**5**	**8**	**6**	**8**	**36**
Mean (SD)	86.10 (11.480)	89.03 (21.068)	82.10 (18.207)	73.93 (10.460)	74.55 (20.127)	79.84 (13.636)	79.85 (15.385)
Median	84.80	85.85	75.50	72.60	71.35	81.40	80.15
Min, Max	68.9, 98.2	67.1, 117.3	65.4, 112.8	60.9, 90.4	43.1, 100.3	62.1, 104.2	43.1, 117.3
Height (cm)							
n	**5**	**4**	**5**	**7**	**6**	**8**	**35**
Mean (SD)	170.6 (8.73)	168.5 (8.66)	167.8 (8.90)	172.0 (11.92)	169.2 (14.54)	169.6 (9.49)	169.8 (10.08)
Median	170.0	167.5	162.0	175.0	170.0	170.0	170.0
Min, Max	162, 183	159, 180	160, 178	147, 183	145, 190	152, 179	145, 190
BMI (kg/m^2)							
n	**5**	**4**	**5**	**7**	**6**	**8**	**35**

Mean (SD)	29.78 (5.100)	31.22 (5.837)	29.49 (8.301)	25.23 (4.887)	25.93 (6.162)	27.66 (3.374)	27.85 (5.537)
Median	31.50	32.44	26.04	24.62	24.70	27.16	26.76
Min, Max	23.8, 36.2	23.8, 36.2	24.1, 44.1	19.4, 32.8	19.1, 33.5	22.0, 32.5	19.1, 44.1
WHO performance status at baseline (n %)							
0	4 (66.7)	3 (75.0)	0	3 (37.5)	1 (16.7)	3 (37.5)	14 (37.8)
1	2 (33.3)	1 (25.0)	4 (80.0)	5 (62.5)	5 (83.3)	4 (50.0)	21 (56.8)
2	0	0	1 (20.0)	0	0	0	1 (2.7)

BMI=body mass index; HF=high fat; LF=low fat; NM=no meal; SD=standard deviation; WHO=World Health Organization

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.

Outcome measures

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**	**5**	**19**	**19**	**19**
	Mean (SD)	6733.48 (1768.629)	6289.46 (1632.482)	233.05 (58.546)	-

	CV% mean	26.27	25.96	25.12	-
	Geo-mean	6543.71	6051.11	225.84	-
	CV% geo-mean	27.52	30.76	26.70	-
	Median	6173.70	6426.53	239.00	6.00
	Min - Max	4481.2 - 9056.0	3070.2 - 8537.4	137.0 - 368.0	3.8 - 8.0
FMI	**N**	**4**	**19**	**19**	**19**
	Mean (SD)	6859.14 (1656.009)	5479.76 (1634.203)	229.58 (67.155)	-
	CV% mean	24.14	29.82	29.25	-
	Geo-mean	6697.56	5249.92	219.35	-
	CV% geo-mean	26.24	30.92	33.00	-
	Median	7002.15	5404.40	230.00	6.00
	Min - Max	4707.1 - 8725.1	3421.2 - 8282.1	111.0 - 358.0	2.0 - 8.0

AUCinf=area under the plasma concentration-time curve from time zero infinity; AUClast=area under the plasma concentration-time curve from time zero to the last measureable sampling time; Cmax=maximum concentration; CSF=clinical service form; CV%=coefficient of variation (%)=(sd/mean)*100; CV% geo-mean=sqrt (exp (variance for log transformed data)-1)*100; exp=exponential function; FMI=final market image; PK=pharmacokinetic; SD=standard deviation; sqrt=square root;Tmax=time to reach maximum concentration

**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) for 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	5	6528.16				
	FMI	4	6837.63	FMI / CSF	1.05	0.80	1.37
AUClast (h.ng/mL)	CSF	19	6024.63				
	FMI	19	5289.95	FMI / CSF	0.88	0.82	0.94

Cmax (ng/mL)	CSF	19	225.87				
	FMI	19	219.84	FMI / CSF	0.97	0.89	1.06
Tmax (h)	CSF	19	6.00				
	FMI	19	6.00	FMI / CSF	0	-2.00	4.00

AUCinf= area under the plasma concentration-time curve from time zero infinity; AUClast=area under the plasma concentration-time curve from time zero to the last measureable sampling time; CI=confidence interval; Cmax=maximum concentration; CSF=clinical service form; FMI=final market image; Geo=geometric; PK=pharmacokinetic; Tmax=time to reach maximum concentration

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."

*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 by food state – Arm 2 (PK set)

Food state	Statistics	AUClast (h.ng/mL)	Cmax (ng/mL)	Tmax (h)
	N	**21**	**21**	**21**
NM				
	Mean (SD)	2183.42 (810.874)	141.71 (56.621)	--
	CV% mean	37.14	39.96	--
	Geo-mean	2002.97	127.70	--
	CV% geo-mean	49.00	55.59	--
	Median	2308.90	150.00	5.83
	Min - Max	565.0 - 3523.0	32.8 - 266.0	2.4 - 26.0
LF				
	Mean (SD)	2317.83 (750.991)	145.28 (48.386)	--
	CV% mean	32.40	33.31	--
	Geo-mean	2195.23	135.88	--
	CV% geo-mean	36.29	42.46	--
	Median	2374.33	140.00	6.12
	Min - Max	817.0 - 4237.2	38.0 - 229.0	4.0 - 8.0
HF				
	Mean (SD)	2219.33 (880.319)	132.40 (53.261)	--
	CV% mean	39.67	40.23	--
	Geo-mean	2067.46	122.08	--
	CV% geo-mean	40.41	44.89	--
	Median	1996.49	122.00	7.08

Min - Max	764.0 - 4362.6	37.7 - 247.0	4.0 - 24.8

AUClast=area under the plasma concentration-time curve from time zero to the last measureable sampling time; Cmax=maximum concentration; CV%=coefficient of variation (%)=(sd/mean)*100; CV% geo-mean=sqrt (exp (variance for log transformed data)-1)*100; exp=exponential function; LF=low fat; HF=high fat; NM=no meal; PK=pharmacokinetic; sqrt=square root; SD=standard deviation; Tmax=time to reach maximum concentration

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% CI	
						Lower	Upper
AUClast (ng.h/mL)	NM	21	1999.85	--	--	--	--
	LF	21	2175.90	LF/NM	1.09	1.00	1.19
	HF	21	2034.38	HF/NM	1.02	0.93	1.11
Cmax (ng/mL)	NM	21	128.08	--	--	--	--
	LF	21	135.62	LF/NM	1.06	0.94	1.19
	HF	21	121.25	HF/NM	0.95	0.84	1.06
Tmax (h)	NM	21	5.83				
	LF	21	6.12	LF/NM	0	-20.03	4.67
	HF	21	7.08	HF/NM	1.25	-3.00	21.77

AUC=area under the curve; CI=confidence interval; Cmax=maximum concentration; Geo-mean=geometric mean; HF=high fat; LF=low fat; NM=no meal; PK=pharmacokinetic; Tmax=time to reach maximum concentration

*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’.

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**	**12**	**5**	**5**
	Mean (SD)	22.89 (9.445)	78.70 (21.690)	1728.00 (344.985)
	CV% mean	41.27	27.56	19.96
	Geo-mean	21.35	76.41	1699.19
	CV% geo-mean	39.34	27.52	21.03
	Median	20.13	80.99	1776.59
	Min - Max	13.1 - 41.6	55.2 - 111.6	1252.5 - 2165.0

FMI	**N**	**12**	**4**	**4**
	Mean (SD)	23.27 (8.001)	76.61 (20.898)	1781.08 (608.131)
	CV% mean	34.39	27.28	34.14
	Geo-mean	22.07	74.65	1715.32
	CV% geo-mean	34.90	26.24	31.15
	Median	22.86	71.46	1540.62
	Min - Max	14.5 - 37.4	57.3 - 106.2	1359.0 - 2684.1

AUC= area under the curve; CL/F=total body clearance; CSF=clinical service form; CV%=coefficient of variation (%)=(sd/mean)*100; CV% geo-mean=sqrt (exp (variance for log transformed data)-1)*100; exp=exponential function; FMI=final market image; PK=pharmacokinetic; SD=standard deviation; sqrt=square root ; T1/2= elimination half-life associated with the terminal slope (z)of a semi-logarithmic concentration-time curve; Vz/F=apparent volume of distribution during terminal phase

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

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

Secondary Outcome Result(s)

Efficacy Results

The response to treatment in Arm 1 and Arm 2 was assessed by the Investigator according to RECIST patient lesion response.

In Arm 1, with 23 patients randomized (17 patients had a post-baseline disease assessment and 6 patients discontinued before the first scheduled tumor assessment), 12 out of 23 patients (52.2%) achieved a response of stable disease (SD), and 5 out of 23 patients (21.7%) had progressive disease (PD). No responses (complete response (CR) or partial response (PR)) were observed.

In Arm 2, with 37 patients randomized (27 patients had a post-baseline disease assessment and 10 patients discontinued before the first scheduled tumor assessment), 1 out of 37 patients (2.7%) had a PR for 114 days before discontinuing due to AEs. Seventeen out of 37 patients (45.9%) achieved a response of SD, 8 out of 37 patients (21.6%) achieved a response of PD, and 1 out of 37 patients (2.7%) had a response of unknown.

Safety Results

Adverse Events by System Organ Class

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

Primary system organ class	All patients N=23 n (%)
Any primary system organ class	**19 (82.6)**
Gastrointestinal disorders	15 (65.2)
Nervous system disorders	7 (30.4)

Metabolism and nutrition disorders	6 (26.1)
General disorders and administration site conditions	5 (21.7)
Investigations	4 (17.4)
Respiratory, thoracic and mediastinal disorders	3 (13.0)
Blood and lymphatic system disorders	2 (8.7)
Infections and infestations	2 (8.7)
Musculoskeletal	2 (8.7)
Psychiatric disorders	2 (8.7)
Renal and urinary disorders	2 (8.7)
Skin and subcutaneous tissue disorders	2 (8.7)
Cardiac disorders	1 (4.3)
Endocrine disorders	1 (4.3)
Hepatobiliary disorders	1 (4.3)
Vascular disorders	1 (4.3)

AE=adverse event
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=37 n (%)
Any primary system organ class	**37 (100)**
Gastrointestinal disorders	30 (81.1)
General disorders and administration site conditions	18 (48.6)
Nervous system disorders	14 (37.8)
Skin and subcutaneous tissue disorders	12 (32.4)
Investigations	12 (32.4)
Musculoskeletal and connective tissue disorders	11 (29.7)
Metabolism and nutrition disorders	10 (27.0)
Respiratory, thoracic and mediastinal disorders	10 (27.0)
Infections and infestations	7 (18.9)
Blood and lymphatic system disorders	5 (13.5)
Renal and urinary disorders	4 (10.8)
Vascular disorders	3 (8.1)
Injury, poisoning and procedural complications	2 (5.4)

Endocrine disorders	2 (5.4)
Eye disorders	1 (2.7)
Hepatobiliary disorders	1 (2.7)
Psychiatric disorders	1 (2.7)

AE=adverse event
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 -entered Cycle 2)

Primary system organ class	All patients N=20 n (%)
Any primary system organ class	20 (100)
Gastrointestinal disorders	17 (85.0)
General disorders & administration site conditions	15 (75.0)
Nervous system disorders	14 (70.0)
Metabolism and nutrition disorders	13 (65.0)
Investigations	12 (60.0)
Respiratory, thoracic & mediastinal disorders	9 (45.0)
Vascular disorders	8 (40.0)
Blood and lymphatic system disorders	7 (35.0)
Hepatobiliary disorders	6 (30.0)
Infections & infestations	6 (30.0)
Musculoskeletal & connective tissue disorders	6 (30.0)
Endocrine disorders	5 (25.0)
Skin & subcutaneous tissue disorders	5 (25.0)
Renal & urinary disorders	4 (20.0)
Cardiac disorders	2 (10.0)
Psychiatric disorders	2 (10.0)
Ear and labyrinth disorders	1 (5.0)
Eye disorders	1 (5.0)
Injury, poisoning and procedural complications	1 (5.0)

AE=adverse event
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)

Primary system organ class	All patients N=27 n (%)
Any primary system organ class	**26 (96.3)**
Gastrointestinal disorders	22 (81.5)
Metabolism and nutrition disorders	19 (70.4)
General disorders & administration site conditions	16 (59.3)
Investigations	16 (59.3)
Skin & subcutaneous tissue disorders	14 (51.9)
Musculoskeletal & connective tissue disorders	12 (44.4)
Nervous system disorders	11 (40.7)
Respiratory, thoracic & mediastinal disorders	9 (33.3)
Eye disorders	6 (22.2)
Vascular disorders	6 (22.2)
Infections & infestations	5 (18.5)
Renal & urinary disorders	3 (11.1)
Blood and lymphatic system disorders	2 (7.4)
Hepatobiliary disorders	2 (7.4)
Endocrine disorders	1 (3.7)
Cardiac disorders	1 (3.7)
Psychiatric disorders	1 (3.7)
Injury, poisoning and procedural complications	1 (3.7)
Reproductive system and breast disorders	1 (3.7)

AE=adverse event
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.

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

Adverse events (occurring with at least 5% incidence for all grades) irrespective of causality by

preferred term and maximum grade during Cycle 1 – Arm 1 (Safety set)

Preferred Term*	All Patients N=23 n (%)
-Any AE	
-Total	19 (82.6)
Grade 1	7 (30.4)
Grade 2	7 (30.4)
Grade 3	4 (17.4)
Grade 4	1 (4.3)
Nausea	
Grade 1	5 (21.7)
Grade 2	1 (4.3)
Grade 3	1 (4.3)
Grade 4	0
Vomiting	
Grade 1	5 (21.7)
Grade 2	1 (4.3)
Grade 3	0
Grade 4	0
Diarrhoea	
Grade 1	4 (17.4)
Grade 2	1 (4.3)
Grade 3	0
Grade 4	0

AE=adverse event

*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 5% incidence for all grades) irrespective of causality, by preferred term and maximum grade during Cycle 1 – Arm 2 (Safety set)

Preferred Term*	All Patients N=37 n (%)

-Any primary system organ class	
-Total	37 (100)
Grade 1	8 (21.6)
Grade 2	12 (32.4)
Grade 3	15 (40.5)
Grade 4	2 (5.4)
Diarrhoea	
Grade 1	16 (43.2)
Grade 2	1 (2.7)
Grade 3	1 (2.7)
Grade 4	0
Nausea	
Grade 1	12 (32.4)
Grade 2	5 (13.5)
Grade 3	0
Grade 4	0
Vomiting	
Grade 1	11 (29.7)
Grade 2	4 (10.8)
Grade 3	1 (2.7)
Grade 4	0
Fatigue	
Grade 1	9 (24.3)
Grade 2	3 (8.1)
Grade 3	1 (2.7)
Grade 4	0
Blood alkaline phosphatase increased	
Grade 1	1 (2.7)
Grade 2	2 (5.4)
Grade 3	6 (16.2)
Grade 4	0
Headache	
Grade 1	3 (8.1)
Grade 2	3 (8.1)
Grade 3	1 (2.7)
Grade 4	0
Gamma-glutamyl transferase increase	
Grade 1	0
Grade 2	1 (2.7)

Grade 3	5 (13.5)
Grade 4	0
Decreased appetite	
Grade 1	2 (5.4)
Grade 2	4 (10.8)
Grade 3	0
Grade 4	0
Pain in extremity	
Grade 1	4 (10.8)
Grade 2	1 (2.7)
Grade 3	0
Grade 4	0
Rash	
Grade 1	2 (5.4)
Grade 2	3 (8.1)
Grade 3	0
Grade 4	0

AE=adverse event
*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)

Preferred Term*	**All Patients, N=20 n (%)**
-Any primary system organ class	
-Total	20 (100)

Grade 1	0
Grade 2	6 (30.0)
Grade 3	11 (55.0)
Grade 4	3 (15.0)
Fatigue	
Grade 1	1 (5.0)
Grade 2	7 (35.0)
Grade 3	4 (20.0)
Grade 4	0
Diarrhoea	
Grade 1	5 (25.0)
Grade 2	5 (25.0)
Grade 3	1 (5.0)
Grade 4	0
Vomiting	
Grade 1	7 (35.0)
Grade 2	2 (10.0)
Grade 3	1 (5.0)
Grade 4	0
Blood alkaline phosphatase increased	
Grade 1	2 (10.0)
Grade 2	4 (20.0)
Grade 3	2 (10.0)
Grade 4	0
Decreased appetite	
Grade 1	1 (5.0)
Grade 2	5 (25.0)
Grade 3	1 (5.0)
Grade 4	0
Nausea	
Grade 1	1 (5.0)
Grade 2	4 (20.0)
Grade 3	1 (5.0)
Grade 4	0
Headache	
Grade 1	5 (25.0)
Grade 2	0
Grade 3	1 (5.0)

Grade 4	0
Abdominal pain	
Grade 1	1 (5.0)
Grade 2	3 (15.0)
Grade 3	1 (5.0)
Grade 4	0
Hypoalbuminaemia	
Grade 1	4 (20.0)
Grade 2	0
Grade 3	1 (5.0)
Grade 4	0
Dizziness	
Grade 1	4 (20.0)
Grade 2	1 (5.0)
Grade 3	0
Grade 4	0
Hypothyroidism	
Grade 1	5 (25.0)
Grade 2	0
Grade 3	0
Grade 4	0
Hypertension	
Grade 1	0
Grade 2	1 (5.0)
Grade 3	3 (15.0)
Grade 4	0
Anaemia	
Grade 1	2 (10.0)
Grade 2	1 (5.0)
Grade 3	1 (5.0)
Grade 4	0
Urinary tract infection	
Grade 1	0
Grade 2	2 (10.0)
Grade 3	2 (10.0)
Grade 4	0
Dysgeusia	

Grade 1	2 (10.0)
Grade 2	2 (10.0)
Grade 3	0
Grade 4	0
Neuropathy Peripheral	
Grade 1	2 (10.0)
Grade 2	2 (10.0)
Grade 3	0
Grade 4	0
Hyperbilirubinaemia	
Grade 1	0
Grade 2	2 (10.0)
Grade 3	0
Grade 4	1 (5.0)
Asthenia	
Grade 1	0
Grade 2	2 (10.0)
Grade 3	1 (5.0)
Grade 4	0
Hypertriglyceridaemia	
Grade 1	2 (10.0)
Grade 2	1 (5.0)
Grade 3	0
Grade 4	0
Blood creatinine increased	
Grade 1	1 (5.0)
Grade 2	1 (5.0)
Grade 3	1 (5.0)
Grade 4	0
Dyspepsia	
Grade 1	3 (15.0)
Grade 2	0
Grade 3	0
Grade 4	0
Weight decreased	
Grade 1	3 (15.0)
Grade 2	0
Grade 3	0
Grade 4	0

Constipation	
Grade 1	0
Grade 2	2 (10.0)
Grade 3	0
Grade 4	0
Sinusitis	
Grade 1	0
Grade 2	2 (10.0)
Grade 3	0
Grade 4	0
Deep vein thrombosis	
Grade 1	0
Grade 2	2 (10.0)
Grade 3	0
Grade 4	0
Pyrexia	
Grade 1	1 (5.0)
Grade 2	0
Grade 3	1 (5.0)
Grade 4	0
Dehydration	
Grade 1	0
Grade 2	1 (5.0)
Grade 3	1 (5.0)
Grade 4	0
Blood bilirubin increased	
Grade 1	1 (5.0)
Grade 2	1 (5.0)
Grade 3	0
Grade 4	0
Dysuria	
Grade 1	1 (5.0)
Grade 2	1 (5.0)
Grade 3	0
Grade 4	0
Hypotension	
Grade 1	1 (5.0)

Grade 2	1 (5.0)
Grade 3	0
Grade 4	0
Thrombocytopenia	
Grade 1	2 (10.0)
Grade 2	0
Grade 3	0
Grade 4	0
Stomatitis	
Grade 1	2 (10.0)
Grade 2	0
Grade 3	0
Grade 4	0
Chest pain	
Grade 1	2 (10.0)
Grade 2	0
Grade 3	0
Grade 4	0
Activated partial thromboplastin time prolonged	
Grade 1	2 (10.0)
Grade 2	0
Grade 3	0
Grade 4	0
Alanine aminotransferase increased	
Grade 1	2 (10.0)
Grade 2	0
Grade 3	0
Grade 4	0
Aspartate aminotransferase increased	
Grade 1	2 (10.0)
Grade 2	0
Grade 3	0
Grade 4	0
Blood potassium increased	
Grade 1	2 (10.0)
Grade 2	0
Grade 3	0
Grade 4	0

Blood urea increased	
Grade 1	2 (10.0)
Grade 2	0
Grade 3	0
Grade 4	0
Platelet count decreased	
Grade 1	2 (10.0)
Grade 2	0
Grade 3	0
Grade 4	0
Cough	
Grade 1	2 (10.0)
Grade 2	0
Grade 3	0
Grade 4	0
Dyspnoea	
Grade 1	2 (10.0)
Grade 2	0
Grade 3	0
Grade 4	0
Night sweats	
Grade 1	2 (10.0)
Grade 2	0
Grade 3	0
Grade 4	0

AE=adverse event

*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 systems organ class, preferred term, and maximum grade during subsequent treatment cycles- Arm 2 (Safety set who entered Cycle 2)

Preferred Term*	**All Patients N=27 n (%)**
-Any primary system organ class	
-Total	26 (96.3)
Grade 1	2 (7.4)
Grade 2	4 (14.8)

Grade 3	20 (74.1)
Grade 4	0
Vomiting	
Grade 1	8 (29.6)
Grade 2	3 (11.1)
Grade 3	3 (11.1)
Grade 4	0
Nausea	
Grade 1	7 (25.9)
Grade 2	3 (11.1)
Grade 3	3 (11.1)
Grade 4	0
Fatigue	
Grade 1	3 (11.1)
Grade 2	5 (18.5)
Grade 3	4 (14.8)
Grade 4	0
Rash	
Grade 1	9 (33.3)
Grade 2	1 (3.7)
Grade 3	1 (3.7)
Grade 4	0
Diarrhoea	
Grade 1	5 (18.5)
Grade 2	4 (14.8)
Grade 3	1 (3.7)
Grade 4	0
Decreased appetite	
Grade 1	5 (18.5)
Grade 2	1 (3.7)
Grade 3	1 (3.7)
Grade 4	0
Hypertriglyceridaemia	
Grade 1	1 (3.7)
Grade 2	3 (11.1)
Grade 3	3 (11.1)
Grade 4	0

Dehydration	
Grade 1	2 (7.4)
Grade 2	1 (3.7)
Grade 3	3 (11.1)
Grade 4	0
Headache	
Grade 1	2 (7.4)
Grade 2	3 (11.1)
Grade 3	1 (3.7)
Grade 4	0
Gamma-glutamyl transferase increased	
Grade 1	1 (3.7)
Grade 2	1 (3.7)
Grade 3	2 (7.4)
Grade 4	0
Blood triglycerides increased	
Grade 1	2 (7.4)
Grade 2	0
Grade 3	2 (7.4)
Grade 4	0
Constipation	
Grade 1	3 (11.1)
Grade 2	0
Grade 3	1 (3.7)
Grade 4	0
Platelet count decreased	
Grade 1	2 (7.4)
Grade 2	2 (7.4)
Grade 3	0
Grade 4	0
Abdominal pain	
Grade 1	1 (3.7)
Grade 2	1 (3.7)
Grade 3	2 (7.4)
Grade 4	0
Hypertension	
Grade 1	1 (3.7)
Grade 2	1 (3.7)

Grade 3	2 (7.4)
Grade 4	0
Dizziness	
Grade 1	3 (11.1)
Grade 2	0
Grade 3	1 (3.7)
Grade 4	0
Pulmonary embolism	
Grade 1	0
Grade 2	0
Grade 3	3 (11.1)
Grade 4	0
Lipase increased	
Grade 1	0
Grade 2	2 (7.4)
Grade 3	1 (3.7)
Grade 4	0
White blood cell count decreased	
Grade 1	0
Grade 2	1 (3.7)
Grade 3	2 (7.4)
Grade 4	0
Pain	
Grade 1	1 (3.7)
Grade 2	1 (3.7)
Grade 3	1 (3.7)
Grade 4	0
Back pain	
Grade 1	1 (3.7)
Grade 2	1 (3.7)
Grade 3	1 (3.7)
Grade 4	0
Pain in extremity	
Grade 1	1 (3.7)
Grade 2	1 (3.7)
Grade 3	1 (3.7)
Grade 4	0
Flank pain	

Grade 1	0
Grade 2	1 (3.7)
Grade 3	2 (7.4)
Grade 4	0
Pyrexia	
Grade 1	2 (7.4)
Grade 2	1 (3.7)
Grade 3	0
Grade 4	0
Musculoskeletal pain	
Grade 1	2 (7.4)
Grade 2	1 (3.7)
Grade 3	0
Grade 4	0
Pruritus	
Grade 1	3 (11.1)
Grade 2	0
Grade 3	0
Grade 4	0

AE=adverse event

*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=23 n (%)**
Adverse events (AEs)	**19 (82.6)**
Grade 3-4 AEs	5 (21.7)
Suspected to be drug-related	1 (4.3)
All deaths	**1 (4.3)**
AEs suspected to be drug-related	**13 (56.5)**
Serious adverse events (SAEs)	**2 (8.7)**
AEs leading to discontinuation	**3 (13.0)**
AEs requiring dose adjustment or interruption	**1 (4.3)**

AE=adverse event; SAE=serious AE

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.

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=20 n (%)
Adverse events (AEs)	20 (100)
Grade 3-4 AEs	14 (70.0)
Suspected to be drug-related	10 (50.0)
All deaths	2 (10.0)
AEs suspected to be drug-related	17 (85.0)
Serious adverse events (SAEs)	7 (35.0)
AEs leading to discontinuation	5 (25.0)
AEs requiring dose adjustment or interruption	9 (45.0)

AE=adverse event; SAE=serious AE

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.

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=37 n (%)
Adverse events (AEs)	37 (100)
Grade 3-4 AEs	17 (45.9)
Suspected to be drug-related	12 (32.4)
All deaths	3 (8.1)
AEs suspected to be drug-related	34 (91.9)
Serious adverse events (SAEs)	4 (10.8)
AEs leading to discontinuation	6 (16.2)
AEs requiring dose interruption and/or reduction	8 (21.6)

AE=adverse event; SAE=serious AE

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.

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=27 n (%)
Adverse events (AEs)	26 (96.3)
Grade 3-4 AEs	20 (74.1)
Suspected to be drug-related	17 (63.0)
All deaths	0
AEs suspected to be drug-related	26 (96.3)
Serious adverse events (SAEs)	13 (48.1)
AEs leading to discontinuation	5 (18.5)
AEs requiring dose adjustment or interruption	14 (51.9)

AE=adverse event; SAE=serious AE

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

Other Relevant Findings

None

Date of Clinical Trial Report

10-May-2013

Date Inclusion on Novartis Clinical Trial Results Database

3-Jun-2013

Date of Latest Update