Sponsor

Novartis

Generic Drug Name

Dovitinib

Trial Indications

Advanced solid tumors, excluding breast cancer

Protocol Number

CTKI258A2119

Protocol Title

A Phase I, multi-center, open-label, drug-drug interaction study to assess the effect of TKI258 on the pharmacokinetics of caffeine, diclofenac, omeprazole and midazolam administered as a four-drug cocktail in patients with advanced solid tumors, excluding breast cancer.

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

Study initiation date: 29-May-2012 (first patient first visit)

Study completion date: 9-Jul-2014 (last patient last visit)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a multi-center, open-label, Phase I study to assess the effects of dovitinib on the PK of the probe drugs, caffeine, diclofenac, omeprazole and midazolam in patients with advanced solid tumors, excluding breast cancer.

The study was divided in two treatment phases: drug-drug interaction phase (DDI-Phase), followed by a Post-DDI-Phase. On Day 1 of the DDI-Phase, patients were administered a single dose of the probe drug cocktail containing caffeine (100 mg), diclofenac (25 mg), omeprazole (20 mg), and midazolam (2 mg). A full PK profile for each probe drug was

collected over the following 24 hours. On Day 2 of DDI-Phase, dovitinib was administered at 500 mg on a 5 days on / 2 days off schedule. On Day 13 of the DDI-Phase (the 5th dose of dovitnib in Week 2) a pre-dose blood sample for assessment of dovitinib trough plasma concentration was collected, after which patients received dovitinib at a dose of 500 mg and a concomitant single dose of the cocktail, followed by collection of a full PK profile of each probe drug. The DDI-Phase Day 13 was selected to ensure that enzyme induction by dovitinib is at a maximum.

Non-evaluable patients could continue to receive dovitinib as detailed in the Post-DDI-Phase. After completion of the DDI-Phase, patients could continue to receive treatment with dovitinib at a dose of 500 mg orally, once daily, on a 5 days on / 2 days off dosing schedule, repeated every 7 days. Treatment with dovitinib was allowed to continue until the patient experienced unacceptable toxicity that precluded further treatment, disease progression, withdrawal of consent, and/or at the discretion of the Investigator.

Centers

Five centers in the United States

Publication

Not applicable

Objectives:

Primary objective:

To evaluate the effects of dovitinib on the pharmacokinetics (PK) of a cocktail of caffeine, diclofenac, omeprazole and midazolam in patients with advanced solid tumors, excluding breast cancer.

Secondary objective:

- To assess the safety and tolerability of dovitinib when administered in patients with advanced solid tumors, excluding breast cancer.
- To evaluate preliminary evidence of antitumor activity of dovitinib in patients with advanced solid tumors, excluding breast cancer.

Test Product, Dose, and Mode of Administration

Study drug was dovitinib 500 mg administered orally, once daily at 500 mg on a 5 days/2 days off schedule. The probe drug cocktail containing caffeine (100 mg), diclofenac (25 mg), omeprazole (20 mg), and midazolam (2 mg) was administered orally.

Statistical Methods

The patients in the respective Pharmacokinetic Analysis Set (PAS) were included in the PK data analysis for each probe substrate.

A formal statistical analysis was conducted to compare the single-dose PK of each of the individual probe drugs (caffeine, diclofenac, omeprazole, and midazolam) co-administered with and without dovitinib 500 mg under a 5 days on/ 2 days off schedule. The single-dose PK parameters (AUClast, AUCinf and Cmax) for each probe were log-transformed and analyzed with a linear mixed effects model. The model included a fixed effect for treatment (probe + dovitinib 500 mg, probe alone) and a random effect for subject. Effects related to time were assumed to be negligible.

The model-based, between-treatment mean differences (probe + dovitinib 500 mg - probe alone) and corresponding two-sided 90% confidence intervals (CIs) were calculated on the log-scale. The between-treatment differences and 90% CIs were then back-transformed to the original scale to obtain the geometric mean ratios (probe + dovitinib 500 mg / probe alone) and corresponding 90% CIs. No adjustment for multiplicity was considered.

Descriptive statistics including n, arithmetic mean, median, standard deviation, geometric mean, coefficient of variation CV (%), geometric CV (%), minimum and maximum were presented for probe (caffeine, diclofenac, omeprazole, and midazolam) concentrations by treatment (cocktail alone, cocktail + dovitinib) and scheduled time point. A graphical presentation of the probe concentration profiles were also provided by treatment using the arithmetic mean (+/- SD) values at each scheduled time point. The respective PAS sets were used.

Plasma concentration data for the probes were listed by treatment (cocktail alone, cocktail + dovitinib) using the FAS.

Descriptive statistics including n, arithmetic mean, median, standard deviation, geometric mean, coefficient of variation CV (%), geometric CV (%), minimum, and maximum were calculated for dovitinib trough on Day 13 and Week 4, Day 5 (Post-DDI-Phase) using PAS for dovitinib.

All probe single-dose pharmacokinetic parameters were summarized by treatment (cocktail alone, cocktail + dovitinib) using descriptive statistics. Since Tmax is generally evaluated using distribution-free methods, median values and ranges were given for this parameter.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria

- Patients who had cytopathologically or histopathologically confirmed diagnosis of an advanced solid tumor, excluding breast cancer, which had progressed despite standard therapy, or for which no standard therapy exists.
- Age ≥ 18 years.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1.
- Patients who had the following laboratory values:
  - Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
  - Platelets ≥ 100×10^9/L

- Hemoglobin ≥ 8.0 g/dL
- Serum total bilirubin ≤ 1.5×upper limit of normal (ULN)
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0×ULN
- Serum creatinine ≤ 1.5×ULN
  or,
  24-hour urine collection creatinine clearance (CrCl) ≥ 30 mL/min/1.73m^2
  (≥ 50 mL/min/1.73m^2 in the presence of proteinuria)
  or,
  Serum creatinine >1.5-3×ULN with calculated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault equation: CrCl = (140−age in years) * (weight in kg) * (0.85 if female) / (72×serum creatinine in mg/dL)

- Urine dipstick reading: Negative for proteinuria or, if documentation of +1 (+2 for patients with renal cell carcinoma (RCC)) results for protein on dipstick reading, then total urinary protein ≤ 500 mg and measured creatinine clearance ≥ 50 mL/min/1.73 m^2 from a 24-hour urine collection.
- Anticipated life expectancy ≥ 3 months.

Key Exclusion criteria

- Patients with brain metastases as assessed by radiologic imaging (e.g., computed tomography (CT) or magnetic resonance imaging (MRI) scan).
- Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention.
- Patients who have received CYP1A2 inducer, CYP2C9/2C19 inducer or CYP3A4 inducer medications within 30 days prior to start study treatment or are expected to receive during the first 14 days after starting the study treatment.
- Patients with a known hypersensitivity to benzodiazepines.
- Patients who have not recovered from previous anti-cancer therapies.
- Patient with impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of TKI258 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
- Patients who have concurrent severe and/or uncontrolled concomitant medical conditions that could compromise participation in the study.
- Female patients who are pregnant or breast-feeding.
- Fertile males or women not willing to use highly effective methods of contraception.

Participant Flow Table

Patient disposition –DDI-Phase completion (FAS)

Disposition	All patients (N=39) n (%)
Completed	30 (76.9)
Discontinued	9 (23.1)
Primary reason for discontinuation	
Adverse event	8 (20.5)
Death	1 (2.6)

Completed refers to the patients completed all procedures/treatments/visits as per protocol during DDI-Phase.

Patient disposition – Post-DDI-Phase completion (FAS)

Disposition	All patients (N=33) n (%)
Discontinued	33 (100)
Primary reason for discontinuation	
Adverse event	9 (27.3)
Progressive disease	20 (60.6)
Subject/guardian decision	2 (6.1)
Study terminated by Sponsor[1]	1 (3.0)
Death	1 (3.0)

N refers to all the patients who entered the Post-DDI-Phase
[1]this patient was moved to another study

Baseline Characteristics

Demographics and other baseline characteristics (FAS)

Demographic variable	All patients (N=39)
Age (years)	
n	39
Mean	61.1
SD	14.01
Median	64.0
[Min, Max]	[25.0, 83.0]
Sex –n (%)	
Male	18 (46.2)
Female	21 (53.8)
Race –n (%)	
Caucasian	35 (89.7)
Black	3 (7.7)

Demographic variable	All patients (N=39)
Other	1 (2.6)
Ethnicity –n (%)	
Hispanic/Latino	2 (5.1)
Mixed Ethnicity	3 (7.7)
Not reported	13 (33.3)
Unknown	7 (17.9)
Other	14 (35.9)
BMI (kg/m^2)	
n	39
Mean	29.2
SD	9.45
Median	28.3
[Min; Max]	[18.0, 66.2]
ECOG performance status –n (%)	
0	19 (48.7)
1	20 (51.3)
Missing	0

The baseline weight (kg) was defined as the last non-missing assessment of weight before the first study drug administration.
BMI was computed using baseline height and weight value for each patient.
BMI (kg/m^2) = weight (kg) / height (m)^2.

Summary of Pharmacokinetic results

Pharmacokinetic parameters of caffeine

Summary of caffeine primary PK parameters (PAS-caffeine)

Treatment	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)
CAF	N	29	20	29
	Mean (SD)	20553.01 (12900.994)	19158.10 (10451.155)	2388.48 (1087.285)
	CV% mean	62.77	54.55	45.52
	Geo-mean	17221.15	16315.27	2160.12
	CV% geo-mean	68.63	67.11	48.85
	Median	16021.95	16431.86	2070.00
	[Min; Max]	[4163.8; 66928.9]	[4693.6; 39452.0]	[892.0; 5090.0]
CAF + TKI	N	29	23	29
	Mean (SD)	897.40 (615.741)	1086.39 (636.457)	547.66 (409.437)
	CV% mean	68.61	58.58	74.76
	Geo-mean	726.46	918.49	442.49
	CV% geo-mean	73.47	66.34	72.37
	Median	576.65	1024.62	430.00
	[Min; Max]	[262.7; 2679.5]	[301.0; 2760.3]	[123.0; 2030.0]

Treatment	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)

n: number of subjects with non-missing values.
CV% = coefficient of variation (%) = (SD/mean)*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100
CAF stands for caffeine and TKI stands for dovitinib.

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

PK Parameter (unit)	Treatment	n[1]	Adjusted Geo-mean	Comparison	Treatment Comparison Geo-mean Ratio	90% CI Lower	90% CI Upper
AUClast (hr*ng/mL)	CAF	29	17221.15				
	CAF+TKI	29	726.46	CAF+TKI:CAF	0.04	0.03	0.05
AUCinf (hr*ng/mL)	CAF	20	16202.07				
	CAF+TKI	23	905.65	CAF+TKI:CAF	0.06	0.04	0.07
Cmax (ng/mL)	CAF	29	2160.12				
	CAF+TKI	29	442.49	CAF+TKI:CAF	0.20	0.17	0.24

n[1] = number of patients with non-missing values; Geo-mean = geometric mean
Adjusted Geo-mean, Geo-mean ratio and 90% CI are all determined from a mixed effect model and back-transformed from log scale.
The model for log transformed PK parameters (AUC and Cmax) includes treatment as a fixed factor and patient as a random factor.
CAF stands for caffeine and TKI stands for dovitinib.

Summary of caffeine secondary PK parameters (PAS-caffeine)

Treatment	Statistics	Tmax (hr)	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)
CAF	n	29	29	20	20
	Mean (SD)	N/A	7.26 (3.856)	7.37 (4.963)	49.18(24.156)
	CV% mean	N/A	53.12	67.33	49.12
	Geo-mean	N/A	6.38	6.13	44.09
	CV% geo-mean	N/A	55.06	67.15	50.91
	Median	0.57	5.86	6.09	40.49
	[Min; Max]	[0.5; 6.0]	[2.5; 16.8]	[2.5; 21.3]	[16.1; 104.5]
CAF + TKI	n	29	25	23	23
	Mean (SD)	N/A	1.21 (0.297)	129.13 (77.222)	210.15 (124.500)
	CV% mean	N/A	24.59	59.80	59.24
	Geo-mean	N/A	1.18	108.88	179.88
	CV% geo-mean	N/A	24.51	66.34	61.65
	Median	0.57	1.17	97.60	179.45
	[Min; Max]	[0.5; 1.2]	[0.8; 1.9]	[36.2; 332.3]	[67.8; 504.6]

n: number of subjects with non-missing values.
CV% = coefficient of variation (%) = (SD/mean)*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.
CAF stands for caffeine and TKI stands for dovitinib.

Pharmacokinetic parameters of diclofenac

Summary of diclofenac primary PK parameters (PAS-diclofenac)

Treatment	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)
DIC	n	27	26	27
	Mean (SD)	721.87 (373.054)	750.51 (377.552)	788.48 (597.085)
	CV% mean	51.68	50.31	75.73
	Geo-mean	626.84	655.61	577.62
	CV% geo-mean	61.50	60.09	101.93
	Median	634.54	666.70	531.00
	[Min; Max]	[148.7; 1628.7]	[164.3; 1644.2]	[107.0; 2340.0]
DIC + TKI	n	27	23	27
	Mean (SD)	799.59 (501.966)	916.94 (527.329)	526.71 (459.285)
	CV% mean	62.78	57.51	87.20
	Geo-mean	664.00	782.71	366.68
	CV% geo-mean	69.91	63.89	112.81
	Median	725.62	785.67	402.00
	[Min; Max]	[202.3; 2157.5]	[244.2; 2188.2]	[73.7; 1910.0]

n: number of subjects with non-missing values.
CV% = coefficient of variation (%) = (SD/mean)*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100
DIC stands for diclofenac and TKI stands for dovitinib.

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

	Table				Treatment Comparison		
						90% CI	
PK Parameter (unit)	Treatment	n[1]	Adjusted Geo-mean	Comparison	Geo-mean Ratio	Lower	Upper
AUClast(hr*ng/mL)	DIC	27	626.84				
	DIC+TKI	27	664.00	DIC+TKI:DIC	1.06	0.86	1.31
AUCinf (hr*ng/mL)	DIC	26	655.22				
	DIC+TKI	23	772.86	DIC+TKI:DIC	1.18	0.94	1.48
Cmax(ng/mL)	DIC	27	577.62				
	DIC+TKI	27	366.68	DIC+TKI:DIC	0.63	0.46	0.87

n[1] = number of patients with non-missing values; Geo-mean = geometric mean,
Adjusted Geo-mean, Geo-mean ratio and 90% CI are all determined from a mixed effect model and back-transformed from log scale.
The model for log transformed PK parameters (AUC and Cmax) includes treatment as a fixed factor and patient as a random factor.
DIC stands for diclofenac and TKI stands for dovitinib.

Summary of diclofenac secondary PK parameters (PAS-diclofenac)

Treatment	Statistics	T1/2 (hr)	Tmax (hr)	Vz/F (L)	CL/F (L/hr)
DIC	n	26	27	26	26
	Mean (SD)	1.64 (0.630)	N/A	98.79 (63.248)	44.72 (29.336)
	CV% mean	38.49	N/A	64.02	65.60
	Geo-mean	1.52	N/A	83.37	38.13
	CV% geo-mean	43.32	N/A	63.93	60.10
	Median	1.60	0.53	73.83	37.50
	[Min; Max]	[0.6; 3.1]	[0.5; 3.0]	[29.4; 289.8]	[15.2; 152.1]
DIC+TKI	n	24	27	23	23
	Mean (SD)	3.00 (1.103)	N/A	134.60 (53.979)	36.68 (20.196)
	CV% mean	36.76	N/A	40.10	55.06
	Geo-mean	2.78	N/A	124.27	31.63
	CV% geo-mean	44.65	N/A	43.45	61.51
	Median	2.98	1.02	124.15	31.82
	[Min; Max]	[0.9; 5.4]	[0.5; 4.1]	[56.2; 246.6]	[11.4; 81.9]

n: number of subjects with non-missing values.
CV% = coefficient of variation (%) = (SD/mean)*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100
DIC stands for diclofenac and TKI stands for dovitinib.

Pharmacokinetic parameters of omeprazole

Summary of omeprazole primary PK parameters (PAS-omeprazole)

Treatment	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)
OMZ	n	27	27	27
	Mean (SD)	2759.59 (2687.536)	2841.22 (2834.294)	772.00 (521.544)
	CV% mean	97.39	99.76	67.56
	Geo-mean	1571.91	1615.73	543.91
	CV% geo-mean	179.26	176.56	136.24
	Median	2034.94	2098.34	733.00
	[Min; Max]	[97.8; 10481.0]	[113.4; 11472.9]	[58.0; 2110.0]
OMZ + TKI	n	27	27	27
	Mean (SD)	1098.17 (1221.235)	1135.06 (1255.670)	395.18 (320.288)
	CV% mean	111.21	110.63	81.05
	Geo-mean	632.43	655.38	267.48
	CV% geo-mean	152.48	151.40	127.06
	Median	517.83	546.90	267.00
	[Min; Max]	[101.4; 5005.5]	[111.4; 5024.3]	[38.0; 1030.0]

Treatment	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)

n: number of subjects with non-missing values.
CV% = coefficient of variation (%) = (SD/mean)*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100
OMZ stands for omeprazole and TKI stands for dovitinib.

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

				Treatment Comparison		90% CI	
PK Parameter (unit)	Treatment	n[1]	Adjusted Geo-mean	Comparison	Geo-mean Ratio	Lower	Upper
AUClast(hr*ng/mL)	OMZ	27	1571.91				
	OMZ+TKI	27	632.43	OMZ+TKI:OMZ	0.40	0.29	0.57
AUCinf (hr*ng/mL)	OMZ	27	1615.73				
	OMZ+TKI	27	655.38	OMZ+TKI:OMZ	0.41	0.29	0.57
Cmax(ng/mL)	OMZ	27	543.91				
	OMZ+TKI	27	267.48	OMZ+TKI:OMZ	0.49	0.35	0.69

n[1]= number of patients with non-missing values; Geo-mean = geometric mean
Adjusted Geo-mean, Geo-mean ratio and 90% CI are all determined from a mixed effect model and back-transformed from log scale.
The model for log transformed PK parameters (AUC and Cmax) includes treatment as a fixed factor and patient as a random factor
OMZ stands for omeprazole and TKI stands for dovitinib.

Summary of omeprazole secondary PK parameters (PAS-omeprazole)

Treatment	Statistics	T1/2 (hr)	Tmax (hr)	Vz/F (L)	CL/F (L/hr)
OMZ	n	27	27	27	27
	Mean (SD)	2.49 (1.582)	N/A	53.08 (63.397)	24.94 (36.483)
	CV% mean	63.63	N/A	119.44	146.29
	Geo-mean	2.06	N/A	36.82	12.38
	CV% geo-mean	69.21	N/A	88.41	176.55
	Median	1.95	0.57	28.16	9.53
	[Min; Max]	[0.7; 6.8]	[0.5; 3.0]	[16.4; 306.0]	[1.7; 176.4]
OMZ+TKI	n	27	27	27	27
	Mean (SD)	1.53 (0.770)	N/A	80.55 (61.640)	50.94 (49.042)
	CV% mean	50.33	N/A	76.53	96.27
	Geo-mean	1.36	N/A	60.22	30.77
	CV% geo-mean	53.60	N/A	93.96	152.54
	Median	1.22	1.03	58.32	36.57
	[Min; Max]	[0.6; 3.0]	[0.5; 3.1]	[16.7; 233.2]	[4.0; 179.6]

Treatment	Statistics	T1/2 (hr)	Tmax (hr)	Vz/F (L)	CL/F (L/hr)

n: number of subjects with non-missing values.
CV% = coefficient of variation (%) = (SD/mean)*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100
OMZ stands for omeprazole and TKI stands for dovitinib.

Pharmacokinetic parameters of midazolam

Summary of midazolam primary PK parameters (PAS-midazolam)

Treatment	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)
MDL	n	27	23	27
	Mean (SD)	63.22 (40.971)	63.68 (38.456)	19.66 (10.418)
	CV% mean	64.81	60.39	52.99
	Geo-mean	52.28	53.62	17.13
	CV% geo-mean	70.38	67.45	58.60
	Median	51.46	53.57	18.40
	[Min; Max]	[12.3; 183.8]	[13.5; 164.6]	[6.6; 43.3]
MDL + TKI	n	27	11	27
	Mean (SD)	156.34 (74.135)	160.06 (82.079)	28.35 (11.233)
	CV% mean	47.42	51.28	39.62
	Geo-mean	137.93	136.65	25.97
	CV% geo-mean	59.66	74.40	47.62
	Median	138.57	150.11	27.30
	[Min; Max]	[25.1; 345.3]	[26.3; 303.4]	[7.7; 50.5]

n: number of subjects with non-missing values.
CV% = coefficient of variation (%) = (SD/mean)*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100
MDL stands for midazolam and TKI stands for dovitinib.

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

					Treatment Comparison		
						90% CI	
PK Parameter (unit)	Treatment	n[1]	Adjusted Geo-mean	Comparison	Geo-mean Ratio	Lower	Upper
AUClast(hr*ng/mL)	MDL	27	52.28				
	MDL+TKI	27	137.93	MDL+TKI:MDL	2.64	2.27	3.07
AUCinf (hr*ng/mL)	MDL	23	54.81				
	MDL+TKI	11	158.42	MDL+TKI:MDL	2.89	2.30	3.64
Cmax(ng/mL)	MDL	27	17.13				
	MDL+TKI	27	25.97	MDL+TKI:MDL	1.52	1.33	1.73

PK Parameter (unit)	Treatment	n[1]	Adjusted Geo-mean	Comparison	Treatment Comparison Geo-mean Ratio	90% CI Lower	90% CI Upper

n[1]= number of patients with non-missing values; Geo-mean = geometric mean.
Adjusted Geo-mean, Geo-mean ratio and 90% CI are all determined from a mixed effect model and back-transformed from log scale.
The model for log transformed PK parameters (AUC and Cmax) includes treatment as a fixed factor and patient as a random factor.
MDL stands for midazolam and TKI stands for dovitinib.

Summary of midazolam secondary PK parameters (PAS-midazolam)

Treatment	Statistics	T1/2 (hr)	Tmax (hr)	Vz/F (L)	CL/F (L/hr)
MDL	n	27	27	23	23
	Mean (SD)	7.98 (3.908)	N/A	389.99 (216.178)	44.75 (30.085)
	CV% mean	48.99	N/A	55.43	67.23
	Geo-mean	7.15	N/A	336.22	37.30
	CV% geo-mean	50.53	N/A	62.02	67.45
	Median	6.93	0.50	373.45	37.34
	[Min; Max]	[2.7; 17.6]	[0.5; 1.1]	[106.0; 907.5]	[12.2; 148.3]
MDL+TKI	n	27	27	11	11
	Mean (SD)	15.30 (7.149)	N/A	235.51 (227.167)	18.97 (19.441)
	CV% mean	46.72	N/A	96.46	102.50
	Geo-mean	13.52	N/A	171.65	14.63
	CV% geo-mean	59.96	N/A	96.96	74.42
	Median	15.88	0.53	180.20	13.32
	[Min; Max]	[2.3; 35.2]	[0.5; 2.1]	[44.1; 860.2]	[6.6; 75.9]

n: number of subjects with non-missing values.
CV% = coefficient of variation (%) = (SD/mean)*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100
MDL stands for midazolam and TKI stands for dovitinib.

Summary of Safety

Safety Results

Adverse Events by System Organ Class

Preferred Term	All Patients (N=39) Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)	All grades n (%)

	All Patients (N=39)					
Preferred Term	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**
Any primary system organ class-Total	1 (2.6)	4 (10.3)	27 (69.2)	7 (17.9)	34 (87.2)	39 (100)
Blood and lymphatic system disorders	8 (20.5)	5 (12.8)	3 (7.7)	0	3 (7.7)	16 (41.0)
Cardiac disorders	6 (15.4)	0	2 (5.1)	0	2 (5.1)	8 (20.5)
Ear and labyrinth disorders	1 (2.6)	0	0	0	0	1 (2.6)
Eye disorders	7 (17.9)	1 (2.6)	0	0	0	8 (20.5)
Gastrointestinal disorders	14 (35.9)	14 (35.9)	8 (20.5)	1 (2.6)	9 (23.1)	37 (94.9)
General disorders and administration site conditions	10 (25.6)	15 (38.5)	4 (10.3)	1 (2.6)	5 (12.8)	30 (76.9)
Hepatobiliary disorders	0	0	1 (2.6)	0	1 (2.6)	1 (2.6)
Immune system disorders	0	1 (2.6)	0	0	0	1 (2.6)
Infection and infestations	6 (15.4)	3 (7.7)	2 (5.1)	1 (2.6)	3 (7.7)	12 (30.8)
Injury, poisoning and procedural complications	2 (5.1)	1 (2.6)	0	0	0	3 (7.7)
Investigations	12 (30.8)	5 (12.8)	8 (20.5)	1 (2.6)	9 (23.1)	26 (66.7)
Metabolism and nutritional disorders	11 (28.2)	11 (28.2)	8 (20.5)	1 (2.6)	9 (23.1)	31 (79.5)
Musculoskeletal and connective tissue disorder	10 (25.6)	4 (10.3)	1 (2.6)	0	1 (2.6)	15 (38.5)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (2.6)	1 (2.6)	0	0	0	2 (5.1)
Nervous system disorders	13 (33.3)	4 (10.3)	3 (7.7)	1 (2.6)	4 (10.3)	21 (53.8)
Psychiatric disorders	11 (28.2)	5 (12.8)	0	1 (2.6)	1 (2.6)	17 (43.6)
Renal and urinary disorders	7 (17.9)	2 (5.1)	2 (5.1)	0	2 (5.1)	11 (28.2)
Respiratory, thoracic and mediastinal disorders	11 (28.2)	5 (12.8)	4 (10.3)	4 (10.3)	8 (20.5)	24 (61.5)
Skin and subcutaneous disorders	8 (20.5)	6 (15.4)	1 (2.6)	0	1 (2.6)	15 (38.5)
Vascular disorders	3 (7.7)	5 (12.8)	3 (7.7)	1 (2.6)	4 (10.3)	12 (30.8)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of all grades column.
A patient with multiple adverse events within a primary system organ class is counted only once in the "-Total" row.
A patient with multiple grades for an AE while on a treatment, is only counted under the maximum grade.
Adverse events occurring more than 30 days after last date of study treatment are not summarized.

Most frequent AEs (at least 10%), regardless of study drug relationship, by preferred term, maximum grade (Safety set)

	All Patients (N=39)				
Preferred Term	**All grades n (%)**	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Total	39 (100.0)	1 (2.6)	4 (10.3)	27 (69.2)	7 (17.9)
Diarrhoea	28 (71.8)	20 (51.3)	8 (20.5)	0	0
Fatigue	27 (69.2)	7 (17.9)	17 (43.6)	3(7.7)	0
Nausea	26 (66.7)	13 (33.3)	13 (33.3)	0	0
Vomiting	24 (61.5)	18 (46.2)	6 (15.4)	0	0
Decreased appetite	19 (48.7)	12 (30.8)	6 (15.4)	1 (2.6)	0
Constipation	13 (33.3)	11 (28.2)	1 (2.6)	1 (2.6)	0
Dyspnoea	12 (30.8)	6 (15.4)	4 (10.3)	1 (2.6)	1 (2.6)
Aspartate aminotransferase increased	11 (28.2)	9 (23.1)	0	2 (5.1)	0
Blood alkaline phosphatase increased	10 (25.6)	7 (17.9)	2 (5.1)	1 (2.6)	0
Dehydration	10 (25.6)	5 (12.8)	5 (12.8)	0	0
Alanine aminotransferase increased	9 (23.1)	8 (20.5)	0	1 (2.6)	0
Anaemia	9 (23.1)	3 (7.7)	5 (12.8)	1 (2.6)	0
Dry mouth	8 (20.5)	8 (20.5)	0	0	0
Headache	8 (20.5)	5 (12.8)	2 (5.1)	1 (2.6)	0
Hypoalbuminaemia	8 (20.5)	2 (5.1)	4 (10.3)	2 (5.1)	0
Thrombocytopenia	8 (20.5)	5 (12.8)	3 (7.7)	0	0
Cough	7 (17.9)	6 (15.4)	1 (2.6)	0	0
Flatulence	7 (17.9)	4 (10.3)	3 (7.7)	0	0
Gamma-glutamyltransferase increased	7 (17.9)	1 (2.6)	2 (5.1)	4 (10.3)	0
Insomnia	7 (17.9)	4 (10.3)	3 (7.7)	0	0
Anxiety	6 (15.4)	6 (15.4)	0	0	0
Hypocalcaemia	6 (15.4)	4 (10.3)	2 (5.1)	0	0
Abdominal pain	5 (12.8)	3 (7.7)	0	2 (5.1)	0
Hypertriglyceridaemia	5 (12.8)	2 (5.1)	1 (2.6)	1 (2.6)	1 (2.6)
Neutropenia	5 (12.8)	3 (7.7)	1 (2.6)	1 (2.6)	0
Oedema peripheral	5 (12.8)	4 (10.3)	1 (2.6)	0	0
Proteinuria	5 (12.8)	4 (10.3)	1 (2.6)	0	0
Tachycardia	5 (12.8)	5 (12.8)	0	0	0
Ascites	4 (10.3)	1 (2.6)	3 (7.7)	0	0
Asthenia	4 (10.3)	1 (2.6)	2 (5.1)	0	1 (2.6)
Deep vein thrombosis	4 (10.3)	0	3 (7.7)	1 (2.6)	0
Hypertension	4 (10.3)	1 (2.6)	0	2 (5.1)	1 (2.6)

Preferred Term	All Patients (N=39) All grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hyponatremia	4 (10.3)	1 (2.6)	0	3 (7.7)	0
Pulmonary embolism	4 (10.3)	0	1 (2.6)	2 (5.1)	1 (2.6)

Includes AEs from DDI-Phase and clinical treatment phase (Post-DDI-Phase) together.
Preferred terms were sorted in descending frequency of all grades column.
A patient with multiple grades for one adverse event while on a treatment was only counted once under the maximum grade.
A patient with multiple adverse events under multiple CTC grades was counted only once for each CTC grade.

Deaths, Serious Adverse Events and AEs leading to study drug discontinuation

Preferred term	All Patients N=39 n (%)
Deaths	6 (15.4)
Serious adverse events	23 (59.0)
AEs requiring study drug discontinuation	15 (38.5)

Other Relevant Findings

None

Conclusion:

- Administration of oral caffeine with multiple doses of dovitinib decreased the geometric mean of AUClast by 96%, AUCinf by 94% and Cmax by 80% of caffeine, this was indicative of dovitinib being a strong CYP1A2 inducer.
- Administration of oral diclofenac with multiple doses of dovitinib increased the geometric mean of AUCinf by 18% and AUClast by 6% of diclofenac and decreased the Cmax by 37%. The overall impact of dovitinib on CYP2C9 was limited and no direct conclusions could be drawn.
- Administration of oral omeprazole with multiple doses of dovitinib decreased the geometric means of AUCinf by 59%, AUClast by 60% and Cmax by 51% of omeprazole, this was indicative of dovitinib being a moderate CYP2C19 inducer.
- Administration of oral midazolam with multiple doses of dovitinib increased the geometric means of AUCinf by 2.6-fold, AUClast by 2.9-fold and Cmax by 52% of midazolam, this was indicative of dovitinib being a moderate CYP3A4/5 inhibitor.
- The study drug was tolerated well by the study population with no major or new safety concerns evaluated in this study.

Date of Clinical Trial Report

16-Apr-2015

Date of Initial Inclusion on Novartis Clinical Trial Results website

16-Jun-2015

Date of Latest Update

Reason for Update