Sponsor

Novartis

Generic Drug Name

Dovitinib

Trial Indication(s)

Cancer patients with normal and impaired hepatic function

Protocol Number

CTKI258A2124

Protocol Title

A multi-center, open-label study to assess pharmacokinetics of TKI258 in adult cancer patients with normal and impaired hepatic function

Clinical Trial Phase

I

Phase of Drug Development

III

Study Start/End Dates

Start date: 14-Nov-2011 (first patient first visit)
End date: 17-Oct-2014 (last patient last visit)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was an open label, multicenter study to assess the PK and safety of dovitinib in cancer patients with impaired hepatic function compared to cancer patients with normal hepatic function. This study was conducted in patients with solid tumors and varying degrees of hepatic impairment, which was based on the National Cancer Institute-Organ Dysfunction Working Group (NCI-ODWG) criteria for hepatic dysfunction. Since dovitinib is genotoxic, the study was carried out in cancer patients (utilizing controls with normal hepatic function) assigned to one of the four treatment groups, namely Treatment Group 1 (normal hepatic function; NOR), Treatment Group 2 (mild hepatic impairment; MLD-400 mg or 500 mg), Treatment Group 3 (moderate hepatic impairment; MOD-400 mg), and Treatment Group 4

(severe hepatic impairment) according to the patients' last total bilirubin level and AST/ALT levels known and available prior to dose administration on Week 1 Day 1. The control group comprised of cancer patients with normal hepatic function, and as far as possible, similar to the patients with hepatic impairment, in terms of age and body weight.

Blood samples were collected at a total of 17 time points (approximately 34 mL) per patient starting on Day 1 of Week 1 for pharmacokinetic analysis for single-dose PK and starting from Day 1 of Week 4 for pharmacokinetic analysis for the steady state. The plasma samples from all patients were assayed for dovitinib concentrations, using a validated liquid chromatography-tandem mass spectrometry assay.

Due to safety and tolerability issues that became apparent during the study in both mild (500 mg and 400 mg dose cohort) and moderate hepatic impairment group (400 mg dose cohort), it was decided that the severe hepatic impairment group should not be opened. Seven (out of 38 enrolled) patients developed DLTs, including 2 from the mild hepatic impairment group (500 mg dose cohort), 2 from the mild hepatic impairment group (400 mg dose cohort), and 3 from the moderate impairment group (400 mg dose cohort). The study was closed as per protocol. Due to limited data available from the study, all objectives of the study were not fully evaluated.

Centers

Belgium (1), Germany (3), Italy (3), Netherlands (2), Singapore (1), United States of America (3)

Publication

None

Objectives:

Primary objective

To evaluate the effects of mild or moderate hepatic impairment versus normal hepatic function on the pharmacokinetics (PK) of dovitinib in patients with advanced solid tumor.

Secondary objectives

- To assess the safety and tolerability of dovitinib administration on a 5 days on/2 days off dosing schedule in adult patients with cancer having mild or moderate hepatic impairment compared to patients with normal hepatic function.
- To assess PK, safety and tolerability of dovitinib administration on a 5 days on/2 days off dosing schedule in adult patients with cancer having severe hepatic impairment.
- To explore the relationship between PK and hepatic functional abnormalities (i.e., bilirubin, alanine aminotransferase (ALT)/aspartate aminotransferase (AST), and Child-Pugh classification) using regression analysis as appropriate.

- To evaluate the preliminary anti-tumor activity of dovitinib in the studied patient population.

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

Dovitinib was supplied as 100 mg hard gelatin capsules. Patients could receive doses between 100 mg/day to 500 mg/day on a 5 days on/2 days off schedule, based upon tolerability, as described in table below:

Permitted TKI258 dose adjustments

TKI258 Dose Level	TKI258 Dose (oral 5 days on/2 days off)				
Starting dose	500 mg	400 mg	300 mg	200 mg (severe hepatic impairment group only)	100 mg (severe hepatic Impairment group only)
1st reduced dose	400 mg	300 mg	200 mg	100 mg	-
2nd reduced dose	300 mg	200 mg	-	-	-

Statistical Methods

Due to insufficient number of evaluable patients in the study, no model-based analysis or other PK-related exploratory analyses were performed.

Study Population: Key Inclusion/Exclusion Criteria

The main inclusion criteria were:

- Patients with histologically or cytologically confirmed solid tumor, excluding breast cancer and lymphoma, that was either refractory to the standard therapy or had no available therapies. Hepatocellular carcinoma patients (HCC) with a diagnosis of advanced HCC
- Eastern Cooperative Oncology Group performance status 0 or 1
- Patients must have met the following criteria for laboratory values:
  - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
  - Platelets $\geq 75 \times 10^9$/L
  - Hemoglobin ≥ 9 g/dL
  - Total bilirubin and ALT/AST levels as per modified NCI-ODWG criteria
  - Serum creatinine ≤ 1.5 x upper limit of normal
  - Urine dipstick reading: Negative for proteinuria or, if documentation of +1 results for protein on dipstick reading, then total urinary protein ≤ 500 mg and measured creatinine clearance ≥ 50 mL/min/1.73 m^3 from a 24 hour urine collection
- Patients with measurable and/or non-measurable lesion(s) as assessed by Computer Tomography Scan or Magnetic Resonance Imaging per RECIST 1.1

- Patient with an anticipated life expectancy of ≥ 3 months

Key Exclusion criteria

- Brain metastases, or another primary malignancy within 3 years prior to starting study drug, or hepatocellular carcinoma with liver transplant
- Treatment with chemotherapy, immunotherapy, hormone therapy, radiotherapy or surgery prior to start of study drug
- Prior treatment with an FGFR inhibitor, or current treatment with anti-coagulants
- History of or active Gilbert syndrome, concurrent portal vein tumor thrombus, inferior vena cava tumor thrombus, or vascular invasion, liver toxicities attributed to prior anti-cancer therapy, biliary obstruction or sepsis
- Impaired cardiac, gastro-intestinal function or pulmonary embolism

Participant Flow Table

Patient disposition by treatment arm – end of treatment phase completion (FAS)

Disposition	NOR-TKI500 N=7 n (%)	MLD-TKI400 N=12 n (%)	MLD-TKI500 N=10 n (%)	MOD-TKI400 N=9 n (%)	All patients N=38 n (%)
Discontinued	7 (100)	12 (100)	10 (100)	9 (100)	38 (100)
Primary reason for end of treatment					
Adverse event	2 (28.6)	5 (41.7)	4 (40.0)	6 (66.7)	17 (44.7)
Physician decision	2 (28.6)	0	0	0	2 (5.3)
Progressive disease	3 (42.9)	4 (33.3)	6 (60.0)	1 (11.1)	14 (36.8)
Study terminated by Sponsor	0	1 (8.3)	0	0	1 (2.6)
Patient/Guardian Decision	0	2 (16.7)	0	2 (22.2)	4 (10.5)

N denotes the number of patients who entered the treatment phase, for each treatment arm.

Patient disposition by treatment arm – study phase completion (FAS)

Disposition	NOR-TKI500 N=7 n (%)	MLD-TKI400 N=12 n (%)	MLD-TKI500 N=10 n (%)	MOD-TKI400 N=9 n (%)	All patients N=38 n (%)
Discontinued	7 (100)	12 (100)	10 (100)	9 (100)	38 (100)
Primary reason for study discontinuation					
Adverse event	0	1 (8.3)	0	0	1 (2.6)
Death	2 (28.6)	2 (16.7)	3 (30.0)	3 (33.3)	10 (26.3)
Lost to follow-Up	1 (14.3)	0	1 (10.0)	2 (22.2)	4 (10.5)

Disposition	NOR-TKI500 N=7 n (%)	MLD-TKI400 N=12 n (%)	MLD-TKI500 N=10 n (%)	MOD-TKI400 N=9 n (%)	All patients N=38 n (%)
New therapy for study indication	1 (14.3)	0	0	0	1 (2.6)
Progressive disease	3 (42.9)	6 (50.0)	6 (60.0)	3 (33.3)	18 (47.4)
Study terminated by sponsor	0	1 (8.3)	0	0	1 (2.6)
Patient/guardian decision	0	2 (16.7)	0	1 (11.1)	3 (7.9)

N denotes the number of patients who entered the study phase completion phase, for each treatment arm.

Baseline Characteristics

Demographic summary by treatment group (FAS)

Demographic Variable	NOR-TKI500 N=7	MLD-TKI400 N=12	MLD-TKI500 N=10	MOD-TKI400 N=9
Age (years)				
n	7	12	10	9
Mean	59.7	56.2	57.9	64.8
SD	3.55	10.56	10.29	8.58
Median	60.0	55.0	59.5	66.0
Minimum	56.0	41.0	33.0	52.0
Maximum	65.0	76.0	72.0	75.0
Age category (years) - n (%)				
<65	6 (85.7)	9 (75.0)	8 (80.0)	4 (44.4)
≥ 65	1 (14.3)	3 (25.0)	2 (20.0)	5 (55.6)
Sex - n (%)				
Male	5 (71.4)	8 (66.7)	7 (70.0)	5 (55.6)
Female	2 (28.6)	4 (33.3)	3 (30.0)	4 (44.4)
Race - n (%)				
Caucasian	6 (85.7)	10 (83.3)	7 (70.0)	7 (77.8)
Black	1 (14.3)	0	0	1 (11.1)
Asian	0	2 (16.7)	3 (30.0)	1 (11.1)
Ethnicity - n (%)				
Hispanic or Latino	1 (14.3)	0	0	3 (33.3)
East Asian	0	1 (8.3)	1 (10.0)	1 (11.1)
Southeast Asian	0	0	1 (10.0)	0
South Asian	0	0	1 (10.0)	0
Unknown	0	1 (8.3)	0	0
Other	6 (85.7)	10 (83.3)	7 (70.0)	5 (55.6)

Demographic Variable	NOR-TKI500 N=7	MLD-TKI400 N=12	MLD-TKI500 N=10	MOD-TKI400 N=9
Weight (kg)				
n	7	11	10	9
Mean	78.3	74.3	71.1	68.5
SD	17.74	19.22	15.49	16.46
Median	82.0	78.0	77.7	75.7
Minimum	44.0	48.0	37.7	47.0
Maximum	101.0	114.3	93.0	95.0
Height (cm)				
n	7	11	10	9
Mean	173.0	169.5	173.8	163.5
SD	10.69	11.15	9.68	10.68
Median	176.0	171.0	174.0	157.5
Minimum	158.0	150.0	161.0	150.0
Maximum	186.0	185.0	197.0	180.0
Body surface area (m^2)				
n	7	11	10	9
Mean	1.9	1.9	1.9	1.8
SD	0.28	0.28	0.25	0.27
Median	2.0	1.9	2.0	1.8
Minimum	1.4	1.5	1.3	1.4
Maximum	2.3	2.4	2.1	2.2
Body mass index (kg/m^2)				
n	7	11	10	9
Mean	26.0	25.7	23.4	25.3
SD	4.45	5.27	4.58	3.78
Median	26.8	24.7	23.6	25.0
Minimum	16.4	16.8	14.5	19.6
Maximum	29.5	35.8	32.2	31.2
ECOG performance status - n (%)				
0	3 (42.9)	7 (58.3)	4 (40.0)	3 (33.3)
1	4 (57.1)	5 (41.7)	6 (60.0)	6 (66.7)

The Baseline weight (kg) was defined as the last non-missing assessment of weight before the first study drug administration.

BMI is calculated using Baseline height and weight value for each patient as BMI (kg/m^2) = weight (kg) / height (m)^2

Body Surface Area: BSA[m^2]=234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000

Summary of Efficacy

Primary Outcome Result(s)

Summary of single dose dovitinib primary PK parameters by treatment arm (Pharmacokinetic Analysis set)

PK variable	Statistics	NOR-TKI500 N=6	MLD-TKI400 N=4	MLD-TKI500 N=10	MOD-TKI400 N=9
AUCinf (hr*ng/mL)	n	4	4	10	6
	Mean (SD)	9779.08 (2838.648)	8672.46 (2637.527)	8919.74 (2650.653)	9935.78 (3086.886)
	CV% mean	29.03	30.41	29.72	31.07
	Geo-mean	9484.89	8349.26	8573.02	9531.83
	CV% geo-mean	28.86	33.40	30.39	32.55
	Median	9173.51	9084.61	8371.60	9757.38
	[Min; Max]	[7303.2; 13466.1]	[5568.8; 10951.8]	[5563.0; 13498.6]	[6885.6; 13637.2]
AUClast (hr*ng/mL)	n	5	4	10	9
	Mean (SD)	9266.68 (2246.399)	7579.44 (2275.352)	8129.84 (2509.867)	9128.55 (4026.089)
	CV% mean	24.24	30.02	30.87	44.10
	Geo-mean	9055.67	7305.58	7780.37	8422.08
	CV% geo-mean	24.24	32.88	32.28	43.96
	Median	9057.22	7678.53	7753.82	7538.23
	[Min; Max]	[6883.0; 12507.8]	[4807.1; 10153.6]	[4930.1; 11794.9]	[4820.2; 17370.5]
Cmax (ng/mL)	n	5	4	10	9
	Mean (SD)	312.40 (67.932)	212.75 (63.683)	270.90 (94.733)	242.64 (98.683)
	CV% mean	21.75	29.93	34.97	40.67
	Geo-mean	306.37	206.60	257.26	222.45
	CV% geo-mean	22.50	27.49	34.36	48.97
	Median	317.00	185.00	254.00	253.00
	[Min; Max]	[243.0; 385.0]	[174.0; 307.0]	[172.0; 449.0]	[94.8; 384.0]

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

CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary of single dose dovitinib secondary PK parameters by treatment arm (PAS)

		NOR-TKI500	MLD-TKI400	MLD-TKI500	MOD-TKI400

PK variable	Statistics	N=6	N=4	N=10	N=9
CL/F (L/hr)	n	4	4	10	7
	Mean (SD)	54.27 (14.568)	49.89 (16.737)	60.66 (17.738)	39.40 (16.822)
	CV% mean	26.85	33.55	29.24	42.69
	Geo-mean	52.72	47.91	58.32	35.65
	CV% geo-mean	28.86	33.40	30.39	55.65
	Median	55.74	45.61	59.86	33.55
	[Min; Max]	[37.1; 68.5]	[36.5; 71.8]	[37.0; 89.9]	[13.4; 58.1]
T1/2 (hr)	n	4	4	10	7
	Mean (SD)	15.62 (2.246)	23.12 (6.773)	19.80 (4.499)	28.29 (13.518)
	CV% mean	14.38	29.29	22.72	47.78
	Geo-mean	15.49	22.39	19.31	26.19
	CV% geo-mean	14.54	29.96	24.66	42.07
	Median	15.64	22.37	21.10	24.12
	[Min; Max]	[13.6; 17.6]	[16.1; 31.7]	[13.5; 25.7]	[15.3; 57.2]
Tmax (hr)	n	5	4	10	9
	Median	4.03	5.00	4.00	4.23
	[Min; Max]	[4.0; 24.1]	[4.0; 6.2]	[2.0; 8.0]	[2.0; 24.0]

CV% = coefficient of variation (%) = sd/mean*100.
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

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

PK variable	Statistics	NOR-TKI500 N=6	MLD-TKI500 N=10	MOD-TKI400 N=9
AUClast (hr*ng/mL)	n	5	6	2
	Mean (SD)	7329.25 (2758.330)	11379.34 (6993.083)	16204.17 (6514.604)
	CV% mean	37.63	61.45	40.20
	Geo-mean	6950.64	9840.82	15535.61
	CV% geo-mean	37.05	65.04	43.17
	Median	6282.21	9778.06	16204.17
	[Min; Max]	[4620.7; 11589.8]	[3892.9; 24550.2]	[11597.6; 20810.7]
Cmax (ng/mL)	n	5	6	2
	Mean (SD)	291.80 (39.733)	390.00 (158.041)	409.50 (21.920)
	CV% mean	13.62	40.52	5.35
	Geo-mean	289.63	364.74	409.21
	CV% geo-mean	13.74	41.54	5.36
	Median	283.00	324.00	409.50
	[Min; Max]	[244.0; 336.0]	[215.0; 599.0]	[394.0; 425.0]

PK variable	Statistics	NOR-TKI500 N=6	MLD-TKI500 N=10	MOD-TKI400 N=9

CV% = coefficient of variation (%) = sd/mean*100.
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.
Note: Treatment groups which do not contribute to events/assessments are not displayed.

Summary of steady-state dovitinib secondary PK parameters by treatment arm (Pharmacokinetic analysis set)

PK variable	Statistics	NOR-TKI500 N=6	MLD-TKI500 N=10	MOD-TKI400 N=9
CL/F (L/hr)	n	5	6	2
	Mean (SD)	118.25 (19.132)	92.71 (44.359)	52.37 (8.558)
	CV% mean	16.18	47.85	16.34
	Geo-mean	117.00	84.70	52.02
	CV% geo-mean	16.44	49.36	16.52
	Median	120.58	88.89	52.37
	[Min; Max]	[94.9; 143.5]	[41.5; 173.8]	[46.3; 58.4]
T1/2 (hr)	n	5	6	2
	Mean (SD)	19.65 (6.788)	21.22 (6.403)	45.09 (35.576)
	CV% mean	34.54	30.17	78.90
	Geo-mean	18.78	20.45	37.42
	CV% geo-mean	34.43	30.64	110.04
	Median	19.08	20.23	45.09
	[Min; Max]	[12.2; 30.4]	[13.3; 31.7]	[19.9; 70.2]
Tmax (hr)	n	5	6	2
	Median	4.08	5.98	6.08
	[Min; Max]	[4.0; 6.3]	[2.0; 7.9]	[6.1; 6.1]

CV% = coefficient of variation (%) = sd/mean*100.
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.
Note: Treatment groups which do not contribute to events/assessments are not displayed.

Summary of Safety

Safety Results

Dose limiting toxicities

Summary of dose limiting toxicity, by treatment arm (Dose-determining set)

DLT	NOR-TKI500 N=5 n (%)	MLD-TKI400 N=5 n (%)	MLD-TKI500 N=6 n (%)	MOD-TKI400 N=3 n (%)	All patients N=19 n (%)
Any DLT	0	2 (40.0)	2 (33.3)	3 (100)	7 (36.8)

DLT	NOR-TKI500 N=5 n (%)	MLD-TKI400 N=5 n (%)	MLD-TKI500 N=6 n (%)	MOD-TKI400 N=3 n (%)	All patients N=19 n (%)
Blood Bilirubin Increased	0	0	0	1 (33.3)	1 (5.3)
Diarrhoea	0	0	1 (16.7)	0	1 (5.3)
Hyperbilirubinaemia	0	1 (20.0)	0	1 (33.3)	2 (10.5)
Rash	0	0	0	1 (33.3)	1 (5.3)
Thrombocytopenia	0	0	1 (16.7)	0	1 (5.3)
Transaminases Increased	0	1 (20.0)	0	0	1 (5.3)

Preferred terms are sorted in descending frequency, as reported in the NOR-TKI500 column.

A patient with multiple occurrences of a DLTs under one treatment arm is counted only once in the AE category for that treatment arm.

MedDRA Version 16.1 has been used for the reporting of adverse events.

Adverse events, regardless of study drug relationship, by primary system organ class, maximum CTC grade and treatment arm – NOR-500 mg group (Safety Set) (N=7)

Primary system organ class	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Any primary system organ class	0	0	7 (100)	0	7 (100)
Blood and lymphatic system disorders	0	1 (14.3)	3 (42.9)	0	4 (57.1)
Cardiac disorders	2 (28.6)	0	0	0	2 (28.6)
Gastrointestinal disorders	1 (14.3)	2 (28.6)	1 (14.3)	0	4 (57.1)
General disorders and administration site conditions	2 (28.6)	1 (14.3)	3 (42.9)	0	6 (85.7)
Infections and infestations	1 (14.3)	1 (14.3)	0	0	2 (28.6)
Investigations	0	2 (28.6)	2 (28.6)	0	4 (57.1)
Metabolism and nutrition disorders	1 (14.3)	0	2 (28.6)	0	3 (42.9)
Musculoskeletal and connective tissue disorders	1 (14.3)	1 (14.3)	2 (28.6)	0	4 (57.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (14.3)	0	0	1 (14.3)
Nervous system disorders	1 (14.3)	2 (28.6)	0	0	3 (42.9)
Respiratory, thoracic and mediastinal disorders	0	0	4 (57.1)	0	4 (57.1)
Skin and subcutaneous tissue disorders	1 (14.3)	0	0	0	1 (14.3)
Vascular disorders	0	0	1 (14.3)	0	1 (14.3)

Primary system organ class	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)

Primary system organ classes are presented alphabetically.

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.

Adverse events, regardless of study drug relationship, by primary system organ class, maximum CTC grade and treatment arm – MLD-400 mg group (Safety Set) (N=12)

Primary system organ class	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Any primary system organ class	1 (8.3)	0	8 (66.7)	3 (25.0)	12 (100)
Blood and lymphatic system disorders	0	0	1 (8.3)	0	1 (8.3)
Cardiac disorders	1 (8.3)	0	0	0	1 (8.3)
Ear and labyrinth disorders	1 (8.3)	0	0	0	1 (8.3)
Eye disorders	1 (8.3)	0	0	0	1 (8.3)
Gastrointestinal disorders	5 (41.7)	4 (33.3)	3 (25.0)	0	12 (100)
General disorders and administration site conditions	3 (25.0)	4 (33.3)	0	0	7 (58.3)
Hepatobiliary disorders	1 (8.3)	0	1 (8.3)	1(8.3)	3 (25.0)
Infections and infestations	1 (8.3)	0	0	0	1 (8.3)
Investigations	0	1 (8.3)	7 (58.3)	1(8.3)	9 (75.0)
Metabolism and nutrition disorders	1 (8.3)	1 (8.3)	0	1(8.3)	3 (25.0)
Musculoskeletal and connective tissue disorders	3 (25.0)	2 (16.7)	0	0	5 (41.7)
Nervous system disorders	1 (8.3)	1 (8.3)	1 (8.3)	1 (8.3)	4 (33.3)
Psychiatric disorders	1 (8.3)	0	0	0	1 (8.3)
Renal and urinary disorders	0	1 (8.3)	0	0	1 (8.3)
Respiratory, thoracic and mediastinal disorders	3 (25.0)	1 (8.3)	1 (8.3)	1 (8.3)	6 (50.0)
Skin and subcutaneous tissue disorders	3 (25.0)	0	0	0	3 (25.0)
Vascular disorders	0	0	1 (8.3)	0	1 (8.3)

Primary system organ classes are presented alphabetically.

A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Adverse events, regardless of study drug relationship, by primary system organ class, maximum CTC grade and treatment arm - MLD-500 mg group (Safety Set) (N=10)

	Grade 1	Grade 2	Grade 3	Grade 4	All grades

Primary system organ class	n (%)	n (%)	n (%)	n (%)	n (%)
Any primary system organ class	0	2 (20.0)	6 (60.0)	2 (20.0)	10 (100)
Blood and lymphatic system disorders	0	1 (10.0)	1 (10.0)	1 (10.0)	3 (30.0)
Eye disorders	1 (10.0)	1 (10.0)	0	0	2 (20.0)
Gastrointestinal disorders	5 (50.0)	2 (20.0)	2 (20.0)	1 (10.0)	10 (100)
General disorders and administration site conditions	2 (20.0)	2 (20.0)	4 (40.0)	0	8 (80.0)
Hepatobiliary disorders	0	1 (10.0)	0	0	1 (10.0)
Infections and infestations	1 (10.0)	1 (10.0)	1 (10.0)	1 (10.0)	4 (40.0)
Injury, poisoning and procedural complications	0	0	1 (10.0)	0	1 (10.0)
Investigations	0	2 (20.0)	3 (30.0)	0	5 (50.0)
Metabolism and nutrition disorders	3 (30.0)	2 (20.0)	1 (10.0)	0	6 (60.0)
Musculoskeletal and connective tissue disorders	1 (10.0)	3 (30.0)	1 (10.0)	0	5 (50.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (10.0)	0	0	0	1 (10.0)
Nervous system disorders	3 (30.0)	0	2 (20.0)	0	5 (50.0)
Renal and urinary disorders	1 (10.0)	1 (10.0)	1 (10.0)	0	3 (30.0)
Reproductive system and breast disorders	1 (10.0)	0	0	0	1 (10.0)
Respiratory, thoracic and mediastinal disorders	1 (10.0)	2 (20.0)	0	0	3 (30.0)
Skin and subcutaneous tissue disorders	1 (10.0)	4 (40.0)	0	0	5 (50.0)
Vascular disorders	0	1 (10.0)	2 (20.0)	0	3 (30.0)

Primary system organ classes are presented alphabetically.

A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Adverse events, regardless of study drug relationship, by primary system organ class, maximum CTC grade and treatment arm – MOD-400 mg group (Safety Set) (N=9)

Primary system organ class	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Any primary system organ class	0	0	7 (77.8)	2 (22.2)	9 (100)
Blood and lymphatic system disorders	0	0	3 (33.3)	1(11.1)	4 (44.4)
Cardiac disorders	0	1 (11.1)	0	0	1 (11.1)
Gastrointestinal disorders	3 (33.3)	2 (22.2)	3 (33.3)	0	8 (88.9)
General disorders and administration site conditions	2 (22.2)	2 (22.2)	3 (33.3)	0	7 (77.8)
Hepatobiliary disorders	0	0	2 (22.2)	1(11.1)	3 (33.3)
Infections and infestations	0	0	0	1(11.1)	1 (11.1)
Investigations	0	1 (11.1)	4 (44.4)	0	5 (55.6)
Metabolism and nutrition disorders	1 (11.1)	2 (22.2)	1 (11.1)	0	4 (44.4)

Primary system organ class	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Musculoskeletal and connective tissue disorders	4 (44.4)	1 (11.1)	0	0	5 (55.6)
Nervous system disorders	3 (33.3)	2 (22.2)	1 (11.1)	0	6 (66.7)
Psychiatric disorders	0	1 (11.1)	0	0	1 (11.1)
Respiratory, thoracic and mediastinal disorders	3 (33.3)	0	0	0	3 (33.3)
Skin and subcutaneous tissue disorders	1 (11.1)	2 (22.2)	2 (22.2)	0	5 (55.6)
Vascular disorders	0	0	2 (22.2)	0	2 (22.2)

Primary system organ classes are presented alphabetically.

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.

Adverse events, regardless of study drug relationship, by preferred term, maximum CTC grade, and treatment arm (at least 20 percent in all grades column) – NOR-500 mg group (Safety Set) (N=7)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Any preferred term	0	0	7 (100)	0	7 (100)
Nausea	3 (42.9)	1 (14.3)	0	0	4 (57.1)
Decreased appetite	1 (14.3)	2 (28.6)	0	0	3 (42.9)
Diarrhoea	3 (42.9)	0	0	0	3 (42.9)
Fatigue	0	1 (14.3)	2 (28.6)	0	3 (42.9)
Musculoskeletal pain	2 (28.6)	0	1 (14.3)	0	3 (42.9)
Vomiting	2 (28.6)	1 (14.3)	0	0	3 (42.9)
Abdominal pain upper	2 (28.6)	0	0	0	2 (28.6)
Aspartate aminotransferase increased	2 (28.6)	0	0	0	2 (28.6)
Blood alkaline phosphatase increased	1 (14.3)	1 (14.3)	0	0	2 (28.6)
Blood bilirubin increased	1 (14.3)	0	1 (14.3)	0	2 (28.6)
Dyspnoea	0	0	2 (28.6)	0	2 (28.6)
Gamma-glutamyltransferase increased	0	1 (14.3)	1 (14.3)	0	2 (28.6)
Neutropenia	0	1 (14.3)	1 (14.3)	0	2 (28.6)
Non-cardiac chest pain	1 (14.3)	1 (14.3)	0	0	2 (28.6)
Stomatitis	1 (14.3)	0	1 (14.3)	0	2 (28.6)
Thrombocytopenia	1 (14.3)	0	1 (14.3)	0	2 (28.6)
Weight decreased	0	2 (28.6)	0	0	2 (28.6)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)

Preferred terms are sorted in descending frequency of all grades column.

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.

Adverse events, regardless of study drug relationship, by preferred term, maximum CTC grade and treatment arm (at least 20 percent in all grades column) - MLD-400 mg group (Safety Set) (N=12)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Any preferred term	1 (8.3)	0	8 (66.7)	3 (25.0)	12 (100)
Nausea	7 (58.3)	1 (8.3)	0	0	8 (66.7)
Abdominal pain	1 (8.3)	4 (33.3)	2 (16.7)	0	7 (58.3)
Diarrhoea	5 (41.7)	2 (16.7)	0	0	7 (58.3)
Vomiting	5 (41.7)	2 (16.7)	0	0	7 (58.3)
Aspartate aminotransferase increased	0	1 (8.3)	3 (25.0)	0	4 (33.3)
Blood bilirubin increased	0	2 (16.7)	2 (16.7)	0	4 (33.3)
Fatigue	2 (16.7)	2 (16.7)	0	0	4 (33.3)
Pyrexia	4 (33.3)	0	0	0	4 (33.3)
Alanine aminotransferase increased	1 (8.3)	1 (8.3)	1 (8.3)	0	3 (25.0)
Oedema peripheral	2 (16.7)	1 (8.3)	0	0	3 (25.0)

Preferred terms are sorted in descending frequency of all grades column.

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.

Adverse events, regardless of study drug relationship, by preferred term, maximum CTC grade and treatment arm (at least 20 percent in all grades column) - MLD-500 mg group (Safety Set) (N=10)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Any preferred term	0	2 (20.0)	6 (60.0)	2 (20.0)	10 (100)
Diarrhoea	5 (50.0)	1 (10.0)	1 (10.0)	0	7 (70.0)
Nausea	5 (50.0)	1 (10.0)	0	0	6 (60.0)
Vomiting	4 (40.0)	1 (10.0)	0	0	5 (50.0)
Dry mouth	4 (40.0)	0	0	0	4 (40.0)
Fatigue	1 (10.0)	1 (10.0)	2 (20.0)	0	4 (40.0)
Abdominal pain	1 (10.0)	2 (20.0)	0	0	3 (30.0)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Alanine aminotransferase increased	0	1 (10.0)	2 (20.0)	0	3 (30.0)
Ascites	2 (20.0)	1 (10.0)	0	0	3 (30.0)
Aspartate aminotransferase increased	0	1 (10.0)	2 (20.0)	0	3 (30.0)
Blood bilirubin increased	1 (10.0)	1 (10.0)	1 (10.0)	0	3 (30.0)
Decreased appetite	2 (20.0)	1 (10.0)	0	0	3 (30.0)
Headache	2 (20.0)	0	1 (10.0)	0	3 (30.0)
Anaemia	0	1 (10.0)	1 (10.0)	0	2 (20.0)
Asthenia	1 (10.0)	0	1 (10.0)	0	2 (20.0)
Constipation	1 (10.0)	1 (10.0)	0	0	2 (20.0)
Hypertension	0	0	2 (20.0)	0	2 (20.0)
Myalgia	2 (20.0)	0	0	0	2 (20.0)
Non-cardiac chest pain	1 (10.0)	1 (10.0)	0	0	2 (20.0)
Oedema peripheral	0	1 (10.0)	1 (10.0)	0	2 (20.0)
Oesophageal varices haemorrhage	0	0	1 (10.0)	1 (10.0)	2 (20.0)
Palmar-plantar erythrodysaesthesia syndrome	0	2 (20.0)	0	0	2 (20.0)
Pyrexia	1 (10.0)	0	1 (10.0)	0	2 (20.0)
Rash	2 (20.0)	0	0	0	2 (20.0)
Thrombocytopenia	0	0	1 (10.0)	1 (10.0)	2 (20.0)

Preferred terms are sorted in descending frequency of all grades column.

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.

Adverse events, regardless of study drug relationship, by preferred term, maximum CTC grade and treatment arm (at least 20 percent in all grades column) - MOD-400 mg group (Safety Set) (N=9)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Any preferred term	0	0	7 (77.8)	2 (22.2)	9 (100)
Diarrhoea	5 (55.6)	0	1 (11.1)	0	6 (66.7)
Blood bilirubin increased	0	2 (22.2)	2 (22.2)	0	4 (44.4)
Fatigue	1 (11.1)	2 (22.2)	1 (11.1)	0	4 (44.4)
Platelet count decreased	1 (11.1)	3 (33.3)	0	0	4 (44.4)
Abdominal pain	2 (22.2)	1 (11.1)	0	0	3 (33.3)
Asthenia	1 (11.1)	0	2 (22.2)	0	3 (33.3)
Headache	3 (33.3)	0	0	0	3 (33.3)
Nausea	2 (22.2)	0	1 (11.1)	0	3 (33.3)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Thrombocytopenia	0	0	2 (22.2)	1 (11.1)	3 (33.3)
Vomiting	1 (11.1)	0	2 (22.2)	0	3 (33.3)
Abdominal pain upper	1 (11.1)	1 (11.1)	0	0	2 (22.2)
Anaemia	0	1 (11.1)	1 (11.1)	0	2 (22.2)
Arthralgia	1 (11.1)	1 (11.1)	0	0	2 (22.2)
Aspartate aminotransferase increased	0	0	2 (22.2)	0	2 (22.2)
Dry mouth	2 (22.2)	0	0	0	2 (22.2)
Dysgeusia	2 (22.2)	0	0	0	2 (22.2)
Dyspepsia	1 (11.1)	1 (11.1)	0	0	2 (22.2)
Hyperbilirubinaemia	0	0	2 (22.2)	0	2 (22.2)
Oedema peripheral	2 (22.2)	0	0	0	2 (22.2)
Pain in extremity	2 (22.2)	0	0	0	2 (22.2)
Pyrexia	1 (11.1)	0	1 (11.1)	0	2 (22.2)
Rash	1 (11.1)	0	1 (11.1)	0	2 (22.2)

Preferred terms are sorted in descending frequency of all grades column.

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.

Serious Adverse Events and Deaths

Serious AEs, regardless of study drug relationship, by preferred term, maximum CTC grade – NOR-500 mg group (Safety Set) (N=7)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Any preferred term	0	0	6 (85.7)	0	6 (85.7)
Aortic dissection	0	0	1 (14.3)	0	1 (14.3)
Decreased appetite	0	1 (14.3)	0	0	1 (14.3)
Dyspnoea	0	0	1 (14.3)	0	1 (14.3)
Dyspnoea exertional	0	0	1 (14.3)	0	1 (14.3)
Fatigue	0	0	1 (14.3)	0	1 (14.3)
Hiccups	0	0	1 (14.3)	0	1 (14.3)
Stomatitis	0	0	1 (14.3)	0	1 (14.3)

Preferred terms are sorted in descending frequency of all grades column.

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.

Serious AEs, regardless of study drug relationship, by preferred term, maximum CTC grade - MLD-400 mg group (Safety Set) (N=12)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Any preferred term	0	1 (8.3)	3 (25.0)	2 (16.7)	6 (50.0)
Abdominal pain	0	0	2 (16.7)	0	2 (16.7)
Acute respiratory failure	0	0	0	1 (8.3)	1 (8.3)
Dehydration	0	0	0	1 (8.3)	1 (8.3)
Depressed level of consciousness	0	0	0	1 (8.3)	1 (8.3)
Dysphagia	0	0	1 (8.3)	0	1 (8.3)
Dyspnoea	0	0	1 (8.3)	0	1 (8.3)
Hyperammonaemia	0	0	0	1 (8.3)	1 (8.3)
Hyperbilirubinaemia	0	0	0	1 (8.3)	1 (8.3)
Nausea	0	1 (8.3)	0	0	1 (8.3)
Neurological decompensation	0	0	1 (8.3)	0	1 (8.3)
Pleural effusion	0	0	1 (8.3)	0	1 (8.3)
Vomiting	0	1 (8.3)	0	0	1 (8.3)

Preferred terms are sorted in descending frequency of all grades column.

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.

Serious AEs, regardless of study drug relationship, by preferred term, maximum CTC grade - MLD-500 mg group (Safety Set) (N=10)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Any preferred term	0	1 (10.0)	4 (40.0)	2 (20.0)	7 (70.0)
Oesophageal varices haemorrhage	0	0	1 (10.0)	1 (10.0)	2 (20.0)
Thrombocytopenia	0	0	1 (10.0)	1 (10.0)	2 (20.0)
Abdominal pain	0	1 (10.0)	0	0	1 (10.0)
Ascites	1 (10.0)	0	0	0	1 (10.0)
Asthenia	0	0	1 (10.0)	0	1 (10.0)
Blood bilirubin increased	0	1 (10.0)	0	0	1 (10.0)
Cerebral haemorrhage	1 (10.0)	0	0	0	1 (10.0)
Dehydration	0	1 (10.0)	0	0	1 (10.0)
Encephalopathy	0	0	1 (10.0)	0	1 (10.0)
Escherichia sepsis	0	0	0	1 (10.0)	1 (10.0)
Fatigue	0	0	1 (10.0)	0	1 (10.0)
Headache	0	0	1 (10.0)	0	1 (10.0)
Oedema peripheral	0	0	1 (10.0)	0	1 (10.0)
Pain in extremity	0	1 (10.0)	0	0	1 (10.0)
Pancytopenia	0	0	1 (10.0)	0	1 (10.0)
Pneumonia	0	0	1 (10.0)	0	1 (10.0)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Presyncope	1 (10.0)	0	0	0	1 (10.0)
Pyrexia	0	0	1 (10.0)	0	1 (10.0)
Renal failure acute	0	1 (10.0)	0	0	1 (10.0)
Urinary tract infection	0	0	1 (10.0)	0	1 (10.0)
Vomiting	1 (10.0)	0	0	0	1 (10.0)

Preferred terms are sorted in descending frequency of all grades column.

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.

Serious AEs, regardless of study drug relationship, by preferred term, maximum CTC grade – MOD-400 mg group (Safety Set) (N=9)

Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Any preferred term	0	0	3 (33.3)	2 (22.2)	5 (55.6)
Pyrexia	1 (11.1)	0	1 (11.1)	0	2 (22.2)
Vomiting	0	0	2 (22.2)	0	2 (22.2)
Aspartate aminotransferase increased	0	0	1 (11.1)	0	1 (11.1)
Bleeding varicose vein	0	0	1 (11.1)	0	1 (11.1)
Blood bilirubin increased	0	0	1 (11.1)	0	1 (11.1)
Cerebral infarction	0	1 (11.1)	0	0	1 (11.1)
Diarrhoea	0	0	1 (11.1)	0	1 (11.1)
Failure to thrive	0	0	1 (11.1)	0	1 (11.1)
Hepatic encephalopathy	0	0	1 (11.1)	0	1 (11.1)
Hepatotoxicity	0	0	0	1 (11.1)	1 (11.1)
Lactic acidosis	0	1 (11.1)	0	0	1 (11.1)
Nausea	0	0	1 (11.1)	0	1 (11.1)
Sepsis	0	0	0	1 (11.1)	1 (11.1)
Thrombocytopenia	0	0	0	1 (11.1)	1 (11.1)
Upper gastrointestinal haemorrhage	0	0	1 (11.1)	0	1 (11.1)

Preferred terms are sorted in descending frequency of all grades column.

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.

On-treatment deaths

On treatment death, by primary system organ class, and preferred term (Safety Set)

Primary system organ class Preferred term	NOR-TKI500 (N=7) n (%)	MLD-TKI400 (N=12) n (%)	MLD-TKI500 (N=10) n (%)	MOD-TKI400 (N=9) n (%)	All patients (N=38) n (%)
Any primary system organ class					
Total	3 (42.9)	1 (8.3)	4 (40.0)	2 (22.2)	10 (26.3)
Gastrointestinal disorders					
Total	0	0	0	1 (11.1)	1 (2.6)
Gastric haemorrhage	0	0	0	1 (11.1)	1 (2.6)
General disorders and administration site conditions					
Total	1 (14.3)	0	1 (10.0)	0	2 (5.3)
Euthanasia	1 (14.3)	0	1 (10.0)	0	2 (5.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)					
Total	2 (28.6)	1 (8.3)	3 (30.0)	1 (11.1)	7 (18.4)
Neoplasm	2 (28.6)	1 (8.3)	3 (30.0)	1 (11.1)	7 (18.4)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency as in the all patients arm

Deaths up to 30 days after the last dose are all included.

Five other patients died after the 30-day post-treatment evaluation period

Other Relevant Findings

Not applicable.

Conclusion:

- Since limited PK data was obtained due to closure of the study before the tolerated dose was identified in any of the hepatic impaired group, no statistical analyses were performed, and no definite conclusions could be derived regarding the pharmacokinetics of dovitinib in mildly and moderately hepatic impairment groups relative to patients with normal hepatic function.
- Based on the results of this study, administration of dovitinib at clinically relevant doses (being 400 and 500 mg a day, 5 days on, 2 days off) to patients with hepatic impairment could result in safety and tolerability concerns.

Date of Clinical Trial Report

25-May-2015

Date of Initial Inclusion on Novartis Clinical Trial Results website

22-Jun-2015

Date of Latest Update

N/A

Reason for Update

N/A