Sponsor

Novartis

Generic Drug Name

Dovitinib (TKI258)

Trial Indication

Advanced solid tumors

Protocol Number

CTKI258A2128

Protocol Title

A phase I, open-label, multi-center, randomized, crossover study to assess the bioequivalence of 2 formulations of TKI258, FMI capsule and FMI tablet, in patients with advanced solid tumors

Clinical Trial Phase

Phase I

Study Start/End Dates

First patient first visit: 05-Dec-2011

Last patient completed: 25-Jul-2014

Study Design/Methodology

This was a Phase I, open-label, multi-center, randomized, two way crossover study to assess the bioequivalence (BE) of dovitinib FMI capsules and FMI tablets in patients with advanced solid tumors, excluding breast cancer. The study consisted of two phases: the BE phase and the post-BE phase. The BE phase consisted of two periods, with a different formulation being taken in each. In both periods, dovitinib was administered at a dose of 500 mg daily on a 5 days on/2 days off dosing schedule. After the completion of the BE phase, patients continued to receive treatment with 500 mg dovitinib FMI capsules daily on a 5 days on/2 days off dosing schedule, repeated every 7 days.

Centers

The study was performed in fourteen centers in the USA.

Publication

None

Objectives:

Primary objective: The primary objective of this study was to assess the bioequivalence (BE) of two formulations of dovitinib, the final market image (FMI) capsule (supplied in 100 mg strength) and FMI tablet (supplied in 250 mg strength), in patients with advanced solid tumors, excluding breast cancer.

Secondary objectives: The secondary objectives of the study were to characterize the safety and tolerability of dovitinib following a 5 days on/2 days off dosing schedule in patients with advanced solid tumors (excluding breast cancer) and to evaluate preliminary evidence of anti-tumor activity of dovitinib in patients with advanced solid tumors (excluding breast cancer).

Test Product, Doses, and Mode of Administration

Dovitinib was supplied by Novartis as 100 mg FMI capsules and 250 mg FMI tablets and was administered orally at a daily dose of 500 mg on a 5 days on/2 days off dosing regimen.

Statistical Methods

Data were presented as summaries, listings and/or plots as appropriate with respect to demographic and baseline characteristics, safety observations and measurements, anti-tumor activity and pharmacokinetic (PK) measurements. Summary statistics for continuous variables include mean, standard deviation (SD), median, minimum, and maximum, unless otherwise specified.

The **full analysis set (FAS)** comprised all patients who were randomized to a study treatment sequence (arm). According to the intent-to-treat principle, patients were analyzed according to the treatment arm they were assigned to during the randomization process.

The **safety set** comprised all patients who received at least one dose of dovitinib.

The **pharmacokinetic analysis set (PAS)** comprised all patients who satisfied the following conditions:

- Provided two evaluable* PK profiles following the administration of 500 mg of FMI capsule and 500 mg of FMI tablet on the days of blood collection for PK profiles
- Did not vomit within the 4 hours after receiving dovitinib on the days of blood collection for PK profiles
- Received $\geq$ 7 of the first 10 scheduled doses of dovitinib at a dose of 500 mg
- Received 4 consecutive days of dosing at 500 mg prior to the days of blood collection for PK profiles
- Did not have any major protocol deviations as specified in Appendix 16.1.9

*For the purpose of being evaluable, a PK profile must have yielded valid AUClast and Cmax, as indicated by the PK parameter exclusion flag provided by the trial pharmacokineticist.

A formal statistical analysis was conducted to assess the bioequivalence of the FMI tablet to the FMI capsule. A linear mixed effects model was fit to the log-transformed parameters (AUClast and Cmax). Included in the model were the formulation, period, and sequence as the fixed effects and patients nested within sequence as random effect.

For the analysis, the tablet was the test formulation and the capsule was the reference. A two-sided 90% CI for the arithmetic mean of the difference (test – reference) on the log-scale was

calculated and the back-transformed 90% CI for the geometric mean of the ratio was provided.

Claiming of BE was based on the PK parameters AUClast and Cmax. If the 90% CIs of the geometric mean ratio for both parameters were completely contained within 0.80-1.25 for test (FMI tablet) versus reference (FMI capsule), then BE was concluded. Unless otherwise specified, the PAS was used for this analysis.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

1. Patients with a histopathologically or cytopathologically confirmed diagnosis of an advanced solid tumor, excluding breast cancer, who have progressed despite standard therapy, or for which no standard therapy exists
2. ECOG performance status 0, 1, or 2
3. Patients must meet protocol-specified laboratory values

Exclusion criteria

1. Patients with brain metastases
2. Patients who have concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study
3. Patients who have not recovered from previous anti-cancer therapies
4. Patients who are expected to receive any prohibited medications during the bioequivalence phase of the study
5. Female patients who are pregnant, breast feeding
6. Fertile male or female of child-bearing potential not willing to use two highly effective methods of contraception

Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow Table

Patient disposition by treatment—BE phase (FAS)

Disposition/Reason	Sequence 1[2] N=88 n (%)	Sequence 2[2] N=85 n (%)	All Patients N=173 n (%)
Completed[1]	39 (44.3)	41 (48.2)	80 (46.2)
Discontinued[1]	49 (55.7)	44 (51.8)	93 (53.8)
Primary reason for not completing study phase			
Adverse event	31 (35.2)	29 (34.1)	60 (34.7)
Patient/guardian decision	6 (6.8)	7 (8.2)	13 (7.5)
Non-compliance with study treatment	5 (5.7)	4 (4.7)	9 (5.2)
Protocol deviation	4 (4.5)	2 (2.4)	6 (3.5)
Progressive disease	1 (1.1)	1 (1.2)	2 (1.2)
Death	2 (2.3)	0	2 (1.2)
Physician decision	0	1 (1.2)	1 (0.6)

[1]Included all randomized patients who completed the BE phase or discontinued during the BE phase
[2]Sequence 1: dovitinib capsule—dovitinib tablet—dovitinib capsule; Sequence 2: dovitinib tablet—dovitinib capsule—dovitinib capsule

Patient disposition in the clinical treatment phase (FAS)

Disposition/Reason	All Patients N[1]=123 n (%)
Discontinued	123 (100.0)
Primary reason for not completing study phase	
Progressive disease	84 (68.3)
Adverse event	21 (17.1)
Patient/guardian decision	8 (6.5)
Physician decision	5 (4.1)
Death	3 (2.4)
Non-compliance with study treatment	2 (1.6)

N[1] = Number of patients entering the clinical treatment phase.

Patient disposition in the study completion phase (FAS)

Disposition/Reason	All patients N[1]=128 n (%)
Completed	97 (75.8)
Discontinued	31 (24.2)
Primary reason for discontinuation	
Lost to follow-up	16 (12.5)
Patient/guardian decision	9 (7.0)
Death	6 (4.7)

N[1] = Number of patients entering the study completion phase

Baseline Characteristics

Demographic and other baseline characteristics by treatment arm (FAS)

Demographic Variable	Sequence 1 N=88	Sequence 2 N=85	All patients N=173
Age (years)			
Mean (SD)	59.5 (10.62)	57.5 (13.65)	58.5 (12.21)
Median	60.0	59.0	60.0
Min-Max	34.0 - 89.0	19.0 - 82.0	19.0 - 89.0
Sex			
Male	42 (47.7)	44 (51.8)	86 (49.7)
Female	46 (52.3)	41 (48.2)	87 (50.3)
Missing	0	0	0
Race			
Caucasian	62 (70.5)	61 (71.8)	123 (71.1)
Black	15 (17.0)	15 (17.6)	30 (17.3)
Asian	6 (6.8)	4 (4.7)	10 (5.8)
Native American	2 (2.3)	1 (1.2)	3 (1.7)
Unknown	2 (2.3)	3 (3.5)	5 (2.9)
Other	1 (1.1)	1 (1.2)	2 (1.2)
Ethnicity			
Hispanic/Latino	11 (12.5)	12 (14.1)	23 (13.3)
Southeast Asian	1 (1.1)	0	1 (0.6)
South Asian	2 (2.3)	0	2 (1.2)
Not reported	16 (18.2)	19 (22.4)	35 (20.2)
Unknown	36 (40.9)	28 (32.9)	64 (37.0)
Other	22 (25.0)	26 (30.6)	48 (27.7)
Missing	0	0	0
Weight (kg)			
Mean (SD)	78.9 (20.65)	81.3 (23.30)	80.1 (21.96)
Median	75.3	80.7	78.1

Min; Max	40.5; 155.3	39.9; 155.9	39.9; 155.9
Height (cm)			
Mean (SD)	169.3 (9.21)	169.0 (11.18)	169.1 (10.20)
Median	170.3	169.0	170.2
Min; Max	148.6; 186.7	139.7; 201.0	139.7; 201.0
BMI (kg/m^2)			
Mean (SD)	27.4 (6.40)	28.3 (6.68)	27.8 (6.54)
Median	26.6	27.8	27.3
Min; Max	16.6; 50.1	16.5; 47.6	16.5; 50.1

The baseline height and weight (kg) were defined as the last non-missing assessment of weight before the first study drug administration.
If the first treatment date was not available, the height and weight measurements at screening were used as baseline
BMI was computed using baseline height and weight value for each patient. BMI (kg/m^2) = weight (kg) / height (m)^2

Summary of Efficacy

Primary Outcome Results

Summary of statistical analysis of primary PK parameters for dovitinib (PAS)

					Formulation Comparison		
						90% CI	
PK Parameter (unit)	**Formulation**	**n[1]**	**Adjusted Geo-mean**	**Comparison(s)**	**Geo-mean Ratio**	**Lower**	**Upper**
AUClast (h*ng/mL)	TKICP	69	5690.78				
	TKITB	69	5383.16	TKITB:TKICP	0.95	0.88	1.01
Cmax (ng/mL)	TKICP	69	252.30				
	TKITB	69	246.77	TKITB:TKICP	0.98	0.91	1.05

n[1] = number of patients with non-missing values; Geo-mean = geometric mean
Geo-mean, Geo-mean ratio and 90% CI were all determined from a mixed effect model and back-transformed from log scale
The model for log transformed PK parameters (AUC and Cmax) included formulation, period and sequence as a fixed factor and patient within sequence as a random factor
TKICP refers to dovitinib FMI capsule formulation and TKITB refers to the FMI tablet formulation

Summary of statistical analysis of primary PK parameters including only the first 48 randomized patients (subset of PAS[1])

					Formulation Comparison		
						90% CI	
PK Parameter (unit)	Formulation	n[1]	Adjusted Geo-mean	Comparison(s)	Geo-mean Ratio	Lower	Upper
AUClast (h*ng/mL)	TKICP	49	5205.25				
	TKITB	49	5050.87	TKITB:TKICP	0.97	0.90	1.05
Cmax (ng/mL)	TKICP	49	235.91				
	TKITB	49	233.57	TKITB:TKICP	0.99	0.91	1.08

[1]Pharmacokinetic analysis subset: a subset of the PAS, including only the first 48 randomized patients. If there were multiple patients having the same randomization date around the 48th rank, all of them are included. Please note: Two patients had the same randomization date, so the actual number of patients is 49 instead of 48.
n[1] = number of patients with non-missing values; Geo-mean = geometric mean
Geo-mean, Geo-mean ratio and 90% CI were all determined from a mixed effect model and back-transformed from log scale
The model for log transformed PK parameters (AUC and Cmax) included formulation, period and sequence as a fixed factor and patient within sequence as a random factor
TKICP refers to dovitinib FMI capsule formulation and TKITB refers to the FMI tablet formulation

Summary of statistical analysis of primary PK parameters excluding patients from Site 1001 (subset of the PAS[1])

					Formulation Comparison		
						90% CI	
PK Parameter (unit)	Formulation	n*	Adjusted Geo-mean	Comparison(s)	Geo-mean Ratio	Lower	Upper
AUClast (h*ng/mL)	TKICP	62	5982.83				
	TKITB	62	5526.39	TKITB:TKICP	0.92	0.86	0.99
Cmax (ng/mL)	TKICP	62	262.88				
	TKITB	62	250.88	TKITB:TKICP	0.95	0.89	1.02

[1]Pharmacokinetic analysis subset: a subset of the PAS, excluding all the patients from site 1001
n* = number of patients with non-missing values; Geo-mean = geometric mean
Geo-mean, Geo-mean ratio and 90% CI were all determined from a mixed effect model and back-transformed from log scale
The model for log transformed PK parameters (AUC and Cmax) included formulation, period and sequence as a fixed factor and patient within sequence as a random factor
TKICP refers to dovitinib FMI capsule formulation and TKITB refers to the FMI tablet formulation

Summary of dovitinib primary PK parameters by formulation (PAS)

Statistics	FMI capsule	FMI tablet
	AUClast (h*ng/mL)	
N	69	69
Mean (SD)	6421.954 (3349.6088)	5909.242 (2697.8791)
CV% mean	52.2	45.7
Geo-mean	5705.392	5378.650
CV% geo-mean	51.9	46.2
Median	5751.940	5590.880
Min-Max	1764.58 - 19828.80	1622.27 - 18093.60
	Cmax (ng/mL)	
N	69	69
Mean (SD)	272.21 (108.794)	266.41 (106.673)
CV% mean	40.0	40.0
Geo-mean	252.14	246.76
CV% geo-mean	41.7	41.5
Median	261.00	258.00
Min-Max	73.4 - 642	80.6 – 671

n: number of patients with non-missing values
CV% = coefficient of variation (%) = (sd/mean)*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Secondary Outcome Results

Summary of dovitinib secondary PK parameters by formulation (PAS)

Statistic	Formulation	AUC0-24h (h*ng/mL)	Clast (ng/mL)	Tmax (h)	Lambda_z (1/h)	T1/2 (h)	CL/F (L/h)	Vz/F (L)
N		69	69	69	69	69	69	69
Mean (SD)	capsule	4245.627 (1856.5555)	16.688 (33.2533)	N/A	0.047 (0.0102)	16.145 (7.7751)	94.669 (50.1230)	1985.092 (864.3821)
	tablet	4064.722 (1568.6606)	10.970 (10.4744)	N/A	0.049 (0.0099)	14.809 (2.9886)	98.988 (47.3537)	2032.345 (924.8550)
CV% mean	capsule	43.7	199	N/A	21.9	48.2	52.9	43.5
	tablet	38.6	95.5	N/A	20.3	20.2	47.8	45.5
Geo-mean	capsule	3891.504	9.459	N/A	0.045	15.323	82.463	1823.070
	tablet	3775.273	8.305	N/A	0.048	14.533	89.490	1876.254
CV% geo-mean	capsule	44.1	113	N/A	30.1	28.2	59.6	43.2
	tablet	41.1	80.9	N/A	21.2	19.5	47.5	40.6
Median	capsule	4014.260	8.420	6.000	0.050	14.390	84.560	1865.030
	tablet	4035.180	7.890	5.080	0.050	14.260	85.840	1922.050
Min; Max	capsule	1254.78; 11610.0	1.63; 263	0; 26.08	0.01; 0.06	11.01; 72.39	13.63; 277.40	673.01; 5005.47
	tablet	1176.43; 9465.00	2.22; 69.8	2.00; 8.17	0.03; 0.07	9.63; 23.19	24.71; 297.48	759.19; 6798.23

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

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

Best overall response per treatment arm for patients with measurable disease at baseline (FAS)

	n (%)	All patients N=173 95% CI
Best response		
Complete response (CR)	0	
Partial response (PR)	1 (0.6)	
Stable disease (SD)	55 (31.8)	
Progressive disease (PD)	48 (27.7)	
Unknown (UNK)	69 (39.9)	
Missing	0	
Overall response rate (ORR: CR + PR)	1 (0.6)	[0, 3.2]
Disease control rate (DCR: CR + PR + SD)	56 (32.4)	[25.2, 39.9]

N: The total number of patients in FAS. It is the denominator for percentage (%) calculation
n: Number of patients who are at the corresponding category
95% CIs are based on Clopper Pearson (exact) method

Summary of Safety

Safety Results

Adverse events regardless of study drug relationship with at least 10% incidence any grade by system organ class and preferred term (Safety set)

	All Patients (N=168)				
Primary system organ class Preferred term	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**All grades n (%)**
Any primary SOC total	**16 (9.5)**	**49 (29.2)**	**84 (50.0)**	**19 (11.3)**	**168 (100.0)**
Blood and lymphatic system disorders total	4 (2.4)	7 (4.2)	13 (7.7)	4 (2.4)	28 (16.7)
Cardiac disorders total	12 (7.1)	3 (1.8)	2 (1.2)	2 (1.2)	19 (11.3)
Gastrointestinal disorders total	74 (44.0)	47 (28.0)	29 (17.3)	0	150 (89.3)
Diarrhoea	82 (48.8)	18 (10.7)	9 (5.4)	0	109 (64.9)
Nausea	68 (40.5)	23 (13.7)	8 (4.8)	0	99 (58.9)
Vomiting	55 (32.7)	16 (9.5)	11 (6.5)	0	82 (48.8)
Abdominal pain	11 (6.5)	10 (6.0)	4 (2.4)	0	25 (14.9)
Constipation	20 (11.9)	3 (1.8)	0	0	23 (13.7)
Dry Mouth	20 (11.9)	0	0	0	20 (11.9)
General disorders and administration site conditions total	42 (25.0)	38 (22.6)	27 (16.1)	2 (1.2)	109 (64.9)
Fatigue	31 (18.5)	34 (20.2)	22 (13.1)	0	87 (51.8)
Infections and infestations total	12 (7.1)	13 (7.7)	9 (5.4)	1 (0.6)	35 (20.8)

	All Patients (N=168)				
Primary system organ class Preferred term	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**All grades n (%)**
Investigations total	21 (12.5)	15 (8.9)	17 (10.1)	3 (1.8)	56 (33.3)
Weight decreased	18 (10.7)	9 (5.4)	1 (0.6)	0	28 (16.7)
Metabolism and nutrition disorders total	29 (17.3)	28 (16.7)	25 (14.9)	5 (3.0)	87 (51.8)
Decreased appetite	31 (18.5)	18 (10.7)	0	0	49 (29.2)
Dehydration	4 (2.4)	15 (8.9)	8 (4.8)	0	27 (16.1)
Hypertriglyceridaemia	2 (1.2)	4 (2.4)	8 (4.8)	4 (2.4)	18 (10.7)
Musculoskeletal and connective tissue disorders total	28 (16.7)	20 (11.9)	6 (3.6)	0 (0.0)	54 (32.1)
Back pain	10 (6.0)	7 (4.2)	1 (0.6)	0	18 (10.7)
Nervous system disorders total	49 (29.2)	12 (7.1)	6 (3.6)	0	67 (39.9)
Headache	17 (10.1)	2 (1.2)	2 (1.2)	0	21 (12.5)
Psychiatric disorders total	17 (10.1)	7 (4.2)	3 (1.8)	0	27 (16.1)
Renal and urinary disorders total	5 (3.0)	8 (4.8)	4 (2.4)	0	17 (10.1)
Respiratory, thoracic and mediastinal disorders total	37 (22.0)	15 (8.9)	13 (7.7)	2 (1.2)	67 (39.9)
Dyspnoea	21 (12.5)	10 (6.0)	3 (1.8)	0	34 (20.2)
Cough	14 (8.3)	3 (1.8)	0	0	17 (10.1)
Skin and subcutaneous tissue disorders total	41 (24.4)	13 (7.7)	3 (1.8)	0	57 (33.9)
Rash	19 (11.3)	4 (2.4)	2 (1.2)	0	25 (14.9)
Vascular disorders total	10 (6.0)	11 (6.5)	19 (11.3)	0	40 (23.8)
Hypertension	2 (1.2)	4 (2.4)	12 (7.1)	0	18 (10.7)

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 AEs within a primary system organ class was counted only once in the total row.

Serious Adverse Events and Deaths

On-treatment death by principal cause—cumulative (Safety set)

Principal cause of death	All patients N=168 n (%)
Total on-treatment deaths	11 (6.5)
Study indication	8 (4.8)
Other	3 (1.8)
Any principal cause of death	
Myocardial infarction	1 (0.6)
Respiratory failure	1 (0.6)
Sepsis	1 (0.6)

Serious adverse events (at least 2% incidence for any grade) irrespective of causality, by preferred term, maximum grade—cumulative (Safety set)

	All Patients (N=168)				
Preferred term	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**All grades n (%)**
Total	**0**	**13 (7.7)**	**43 (25.6)**	**12 (7.1)**	**68 (40.5)**
Vomiting	1 (0.6)	2 (1.2)	6 (3.6)	0	9 (5.4)
Deep vein thrombosis	0	4 (2.4)	3 (1.8)	0	7 (4.2)
Dehydration	1 (0.6)	0	6 (3.6)	0	7 (4.2)
Diarrhoea	0	0	6 (3.6)	0	6 (3.6)
Dyspnoea	0	2 (1.2)	3 (1.8)	0	5 (3.0)
Nausea	0	1 (0.6)	4 (2.4)	0	5 (3.0)
Pleural effusion	0	2 (1.2)	3 (1.8)	0	5 (3.0)
Pulmonary embolism	0	0	5 (3.0)	0	5 (3.0)
Abdominal pain	0	1 (0.6)	3 (1.8)	0	4 (2.4)
Hypotension	0	1 (0.6)	3 (1.8)	0	4 (2.4)
Renal failure acute	1 (0.6)	1 (0.6)	2 (1.2)	0	4 (2.4)
Sepsis	0	0	3 (1.8)	1 (0.6)	4 (2.4)

Cumulative phase includes BE phase and Post-BE Phase together
Preferred terms are sorted in descending frequency of all grades column
A patient with multiple occurrences of an AE is counted only once in the AE category
A patient with multiple grade ratings for an AE is only counted under the maximum rating
A patient with multiple AEs is counted only once in the total row at maximum severity grade

Adverse events (at least 2% incidence for any grade) irrespective of causality, leading to study drug discontinuation by system organ class, preferred term—cumulative (Safety set)

	All Patients (N=168)				
Primary system organ class Preferred term	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**All Grades n (%)**
Any primary SOC total	1 (0.6)	18 (10.7)	32 (19.0)	6 (3.6)	57 (33.9)
Blood and lymphatic system disorders total	0	1 (0.6)	1 (0.6)	2 (1.2)	4 (2.4)
Cardiac disorders total	0	1 (0.6)	1 (0.6)	2 (1.2)	4 (2.4)
Gastrointestinal disorders total	2 (1.2)	6 (3.6)	11 (6.5)	0	19 (11.3)
Vomiting	0	2 (1.2)	5 (3.0)	0	7 (4.2)
Diarrhoea	1 (0.6)	0	3 (1.8)	0	4 (2.4)
Nausea	0	2 (1.2)	2 (1.2)	0	4 (2.4)
General disorders and administration site conditions total	1 (0.6)	5 (3.0)	8 (4.8)	1 (0.6)	15 (8.9)
Fatigue	1 (0.6)	4 (2.4)	8 (4.8)	0	13 (7.7)
Infections and infestations total	1 (0.6)	0	2 (1.2)	1 (0.6)	4 (2.4)
Musculoskeletal and connective tissue disorders total	0	4 (2.4)	2 (1.2)	0	6 (3.6)
Respiratory, thoracic and mediastinal disorders total	1 (0.6)	3 (1.8)	5 (3.0)	0	9 (5.4)
Dyspnoea	0	2 (1.2)	2 (1.2)	0	4 (2.4)

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 AEs within a primary system organ class is counted only once in the total row.

Clinically notable adverse events irrespective of causality by group and preferred term (safety set)

	N=168				
Group Preferred term	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any grade n (%)**
Diarrhea					
Total	80 (47.6)	18 (10.7)	9 (5.4)	0	107 (63.7)
Diarrhoea	80 (47.6)	18 (10.7)	9 (5.4)	0	107 (63.7)
Fatigue/Asthenia					
Total	33 (19.6)	31 (18.5)	21 (12.5)	0	85 (50.6)
Fatigue	32 (19.0)	31 (18.5)	20 (11.9)	0	83 (49.4)
Asthenia	2 (1.2)	3 (1.8)	2 (1.2)	0	7 (4.2)
Severe nausea and vomiting[1]					
Total					30 (17.9)
Nausea					25 (14.9)
Vomiting					19 (11.3)
Retching					1 (0.6)
Torsade de points/QT					

Group Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Any grade n (%)
			N=168		
prolongation					
Total	1 (0.6)	3 (1.8)	1 (0.6)	0	5 (3.0)
Arrhythmia	1 (0.6)	1 (0.6)	0	0	2 (1.2)
Syncope	0	1 (0.6)	1 (0.6)	0	2 (1.2)
Convulsion	0	1 (0.6)	0	0	1 (0.6)
Hand and foot syndrome					
Total	3 (1.8)	1 (0.6)	0	0	4 (2.4)
Palmar-plantar erythrodysaesthesia syndrome	3 (1.8)	1 (0.6)	0	0	4 (2.4)
Left-sided heart failure					
Total	0	3 (1.8)	1 (0.6)	0	4 (2.4)
Ejection fraction decreased	0	2 (1.2)	1 (0.6)	0	3 (1.8)
Pulmonary congestion	0	1 (0.6)	0	0	1 (0.6)
Cholestatic injury					
Total	2 (1.2)	0	0	1 (0.6)	3 (1.8)
Jaundice	1 (0.6)	1 (0.6)	0	0	2 (1.2)
Hyperbilirubinaemia	0	0	0	1 (0.6)	1 (0.6)
Ocular icterus	1 (0.6)	0	0	0	1 (0.6)
Hepatic failure					
Total	0	0	0	1 (0.6)	1 (0.6)
Acute hepatic failure	0	0	0	1 (0.6)	1 (0.6)

Clinically notable AE groups were sorted by descending frequency of total any grade; preferred terms were sorted by descending frequency of any grade within a group of clinically notable AE
A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment
A patient with multiple grades for an AE while on a treatment, was only counted under the maximum grade
AEss occurring more than 30 days after last date of study treatment were not summarized
AEs were graded according to the CTCAE V4.03. MedDRA version 15.1 was used
[1]Frequency of patients with 'Severe nausea and vomiting' was presented only under 'Any grade' column, since CTC grades could not be assigned. Missing grades were included under 'Any grade' column

Other Relevant Findings

Summary of ALT, AST, alkaline phosphatase, and total bilirubin abnormalities (Safety set)

Categories	All patients N=168 n (%)
AST >3 x ULN or ALT >3 x ULN	15 (8.9)
Total bilirubin >2 x ULN and ALT >3 x ULN	1 (0.6)
Total bilirubin >2 x ULN and AST >3 x ULN	3 (1.8)
Total bilirubin >2 x ULN and (ALT >3 x ULN or AST >3 x ULN)	4 (2.4)
Total bilirubin >2 x ULN and alkaline phosphatase ≥ 2 x ULN and (ALT >3 x ULN or AST >3 x ULN)	4 (2.4)
Total bilirubin >2 x ULN and alkaline phosphatase <2 x ULN and (ALT >3 x ULN or AST >3 x ULN)	0
Total bilirubin >2 x ULN and alkaline phosphatase ≥ 2 x ULN and (ALT ≤ 3 x ULN and AST ≤ 3 x ULN)	0

Categories were based on worst post-baseline value for any specific parameter
Categories with multiple parameters were based on worst post-baseline value for each parameter
Baseline was defined as the last non-missing value prior to or on start date of study treatment before the first dose
n = number of patients who satisfied the criteria. Percentage was based on N

Patients with notable ECG intervals (Safety set)

	All patients N=168	
	Total	N (%)
QTcF (ms)		
New >450	126	8 (6.3)
New >480	133	0
New >500	133	0
Increase from baseline >30	133	9 (6.8)
Increase from baseline >60	133	2 (1.5)
QTcB (ms)		
New >450	114	20 (17.5)
New >480	132	2 (1.5)
New >500	133	1 (0.8)
Increase from baseline >30	133	19 (14.3)
Increase from baseline >60	133	3 (2.3)

New = newly occurring post baseline value
Total = number of patients at risk for a specific category. For new abnormal post baseline values,this was the number of patients with both baseline and post baseline values,and baseline not meeting the criteria. For abnormal change from baseline, this was the number of patients with both baseline and post baseline evaluations
n = the number of patients meeting the criteria at least once
Baseline was defined as the average of all ECG measurements taken prior to the first dosing of study medication. When dosing time was missing to determine whether a measurement was collected pre-dose or post- dose, the average of scheduled pre-dose measurements (if available) were used as baseline value
Change from baseline: post baseline – baseline
Unscheduled visits were included

Conclusion:

This study demonstrated that the dovitinib FMI capsule and FMI tablet formulations were bioequivalent.

No new safety concerns emerged during the conduct of this study. Dovitinib was generally safe and tolerated, and safety observations were consistent with previously reported data with dovitinib.

Date of Clinical Trial Report

23-Feb-2015

Date of Initial Inclusion on Novartis Clinical Trial Results website

25-Feb-2015

Date of Latest Update

Reason for Update