Sponsor

Novartis

Generic Drug Name

Everolimus

Therapeutic Area of Trial

Impaired hepatic function

Approved Indications

- Approved for Progressive Neuroendocrine Tumors of Pancreatic Origin (PNET) in unresectable, locally advanced or metastatic disease.
- Approved for Subependymal Giant Cell Astrocytoma (SEGA) associated with Tuberous Sclerosis (TS) that cannot be surgically removed.
- Approved for Advanced Renal Cell Carcinoma after Failure of Treatment Failure with Sunitinib or Sorafenib.

Study Number

CRAD001X2102

Title

An open-label, single-dose study to assess the pharmacokinetics of oral everolimus in subjects with impaired hepatic function

Phase of Development

Phase I

Study Start/End Dates

11 Nov 2009 to 18 Nov 2010

Study Design/Methodology

An open-label, single-dose study to assess the pharmacokinetics (PK) of everolimus in subjects with impaired hepatic function and healthy subjects. Healthy volunteers and subjects with hepatic impairment were enrolled into 4 groups: normal hepatic function (Control group), mild impairment (Child-Pugh A), moderate impairment (Child-Pugh B), and severe impairment (Child-Pugh C). All subjects were administered a single-dose of 10 mg everolimus. Subjects considered non-evaluable for the PK evaluation by Novartis and/or the Principal Investigator were replaced by a

new subject in the same group. All subject groups were enrolled and dosed in parallel. The subjects checked-in to the center on Day −1 (Baseline Visit) and stayed overnight at the center as inpatients for the next three nights (Day −1, Day 1 and Day 2). Subjects returned to the center as outpatients every day from Day 4 until end of study evaluations (EOS) on Day 8. All subjects received a single-dose of everolimus 10 mg on Day 1. Blood sampling for PK evaluations were performed at specified time-points (18 in total): one pre-dose sample < 5 minutes prior to administration of study drug and 17 post-dose samples at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 48.0, 72.0, 96.0, 120.0, 144.0, and 168.0 hours after administration of study drug. Follow-up phone calls were made by study site personnel to subjects after completion of EOS evaluations for collecting safety information.

Centres

Total 3 centres with 1 centre each in Germany, Singapore, and Russia

Publication

None

Objectives

Primary objective(s)

- To evaluate the pharmacokinetics (PK) of a single oral dose of everolimus in subjects with severely impaired hepatic function (Child-Pugh C) relative to healthy controls.

Secondary objective(s)

- To evaluate the PK of a single oral dose of everolimus in subjects with mild and moderate hepatic impairment (Child-Pugh A and B, respectively) relative to healthy controls.
- To assess the safety and tolerability of a single-dose of everolimus in subjects with impaired hepatic function (Child-Pugh classes A, B, and C).
- To explore the relationship between PK and hepatic function parameters.

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

Everolimus 10 mg (two 5 mg tablets) single dose orally. All subjects received the same light low-fat breakfast on Day 1 prior to dose administration.

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

None

Criteria for Evaluation

Primary variables

Everolimus concentration in whole blood was determined by a LC-MS method following liquid extraction. The method has a lower limit of quantification (LLOQ) of 0.300 ng/mL. The PK parameters were determined in serum using noncompartmental methods.

Secondary variables

None

Safety and tolerability

Safety assessments consisted of collecting all adverse events (AEs) and serious adverse events (SAEs) with their severity and relationship to study drug, pregnancy test and regular monitoring of hematology, serum chemistry, urine, vital signs, ECGs, physical condition, height and body weight.

Pharmacology

As discussed under primary variables

Statistical Methods

Pharmacokinetic parameters were determined using non-compartmental method(s) using WinNonlin® Pro (Version 5.0).

Primary: $AUC_{(0\text{-}inf)}$ and C_{max}.

Secondary PK: $AUC_{(0\text{-}tlast)}$, T_{max}, λ_z, Vd/F, CL/F, CL/F normalized by body surface area (BSA) and $T_{1/2}$.

No formal statistical hypothesis was tested.

PK parameters ($AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}tlast)}$, C_{max}, CL/F, and CL/F normalized by BSA) were analyzed-separately on the log scale by means of an ANOVA model including hepatic impairment group (Child-Pugh A, B and C and normal hepatic function) as a fixed effect. The geometric mean PK parameter and its 90% confidence interval (CI) were derived from the model for each hepatic impairment group and for the control group. Contrasts were constructed to compare hepatic-impaired groups with the control group. In particular contrasts were estimated for healthy volunteers (control group) versus each hepatic impairment group (Child-Pugh A, B or C). The geometric mean ratios and their 90% CI were derived by back-transformation of estimates of the differences and their CIs. For T_{max} difference between treatments, a non-parametric analysis (Hodges-Lehmann) was performed to provide the estimate of the median difference and its corresponding asymptotic two-sided 90% CI. In particular, median differences were estimated for normal group versus hepatic impairment group (Child-Pugh A, B or C).

All PK parameters were descriptively summarized by hepatic function group. Descriptive statis-

tics of PK parameters included mean, median, standard deviation (SD), CV, geometric mean and geometric CV and range. For T_{max} median and ranges were given. The same analysis performed for the primary objective was used to evaluate the PK of a single oral dose of everolimus in subjects with mild and moderate hepatic impairment (Child-Pugh A and B, respectively) relative to healthy subjects.

Exploratory analysis: The relationship between the PK parameters ($AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}tlast)}$, C_{max}) and hepatic function was investigated by separate linear regression models predicting the individual's log transformed PK parameter by the log-transformed hepatic function test results (International normalized ratio [INR], bilirubin and albumin levels as well as ALT and AST) on Day 4. The regression coefficients representing the relationship between the PK parameters and the hepatic function parameters were estimated together with its 90% CI. The linear model was performed on non log transformed values as well.

Post-hoc analyses: Post-hoc analyses were performed to determine the threshold values of the liver function parameters bilirubin, albumin, and INR (based on Day 4 laboratory values) for potential guidance in dose modification recommendations for everolimus in hepatic impaired subjects (based on Day 8 Child-Pugh status). From the linear model results, expected mean $AUC_{(0\text{-}inf)}$ and its 90% CI were estimated for each bilirubin level (respectively albumin and INR values). A linear regression model was tested between log-transformed bilirubin values and $\log(AUC_{(0\text{-}inf)})$, showing a higher r-square (r_2=0.66), hence this model on log-transformed values was used to determine the threshold values. Albumin and INR, were not log-transformed to determine the threshold values. Bilirubin, albumin and INR values associated with 2-fold and 3-fold increases in AUC (based on upper bound of the 90% CI of expected mean) was designated as the threshold values for 2-fold and 3-fold reductions in everolimus dose, respectively. The threshold values of 2-fold and 3-fold reduction in everolimus dose were 15.0 µmol/L (0.877 mg/dL) and 34.8 µmol/L (2.035 mg/dL) for bilirubin, 43.1 g/L and 37.6 g/L for albumin, and 1.1 and 1.3 for INR, respectively.

Safety was mainly summarized by the incidence (number and percentage) of all the treatmente-mergent AEs and SAEs. Laboratory data was summarized by group (Child-Pugh A, B and C and normal hepatic function), by shift tables, by change from baseline values, and by the flagging of notable values (CTC Grades 1 − 4). Other safety data (e.g. ECG, vital signs, and special tests) was summarized as appropriate.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

All Groups

- Male or female subjects between 18 − 75 years.
- Subjects in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests of no medical significance at screening (except for hepatic impaired subjects) For hepatic impaired subjects, some tests results may reflect their hepatic insufficiency as outlined in additional inclusion criteria for hepatic impaired subjects (Groups 2, 3, 4) below.
- All females of child-bearing potential had to have a negative pregnancy test result at screening and at baseline. Sexually active pre-menopausal women had to use highly effective contraceptive measures while they were enrolled in the study and until 8 weeks after the last exposure to everolimus**.**

- Vital signs (after 3 minutes resting measured in the supine position) within the following ranges:
  - Oral body temperature between 36.0 − 37.5°C
  - Systolic blood pressure < 130 mmHg
  - Diastolic blood pressure < 85 mmHg
  - Pulse rate 60-100 beats per minute (bpm)
- Subjects had to weigh at least 50 kg.
- Subjects were able to provide written informed consent prior to study participation and agreed to be available for the extent of the study.

Hepatic impairment subjects (Groups 2, 3, 4)

Additional inclusion criteria:

- A Child-Pugh score clinically determined and calculated as per the Child-Pugh classificationChild-Pugh A (Group 2) or B (Group 3) or C (Group 4).
- Absolute neutrophil count (ANC) > 1000 cells/mm^3.
- Hemoglobin (Hb) > 9 mg/mL.
- Platelet count > 50,000/ mm^3 at screening and baseline.
- Serum creatinine ≤ 2.0 × upper limit of normal (ULN).
- Free of significant medical disorders unrelated to the subject's hepatic disorder.

Exclusion Criteria:

All Groups

- Participation in any clinical investigation within 4 weeks prior to dosing or longer if required by local regulation.
- Donation or loss of 400 mL or more of blood within 8 weeks prior to dosing.
- Pregnant or nursing females.
- Significant illness, including infections, or hospitalization within the 4 weeks prior to dosing (except for hepatic impaired subjects who due to their liver disease may be affected by significant medical problems which require frequent hospitalizations). Invasive systemic fungal infections were to be fully resolved prior to study entry.
- History of acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated).
- History of clinically significant drug allergy; history of atopic allergy (asthma, urticaria, eczematous dermatitis). A known hypersensitivity to the study drug (everolimus) or drugs similar to the study drug (other mTOR inhibitors, e.g., rapamycin or temsirolimus).
- Active bleeding during the last 28 days prior to dosing including variceal bleeding.
- Except for hepatic impairment, any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs. The investigator was to be guided by evidence of any of the following:
  - History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection.
- Known history of HIV seropositivity.

- Use of tobacco within 7 days prior to dosing or during the study.
- Consumption of alcohol within 3 days prior to dosing or during the study.
- Consumption of grapefruits, grapefruit juice, Seville oranges, starfruit or related foods within 7 days prior to dosing or during the study period.
- Use of any drugs (prescription and non-prescription) known to affect CYP3A4 or PgP, including both inhibitors and inducers, within 7 days prior to dosing or during the study, except for medication which could be required to treat the subject's current liver disease.

Healthy volunteers (Group 1)

Additional exclusion criteria:

- A positive Hepatitis B or Hepatitis C test result.
- Use of drugs (prescription or non-prescription) known to affect CYP3A4 or PgP, including both inhibitors and inducers 14 days prior to dosing.
- History of smoking, drug or alcohol abuse within the 6 months prior to dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening or baseline evaluations.

Hepatic impairment subjects (Groups 2, 3, 4)

Additional exclusion criterion:

- Symptoms or history of Grade 3 or 4 hepatic encephalopathy within 4 weeks of study entry.

Number of Subjects

Subject disposition by hepatic impairment status based on Child-Pugh classification at baseline (FAS)

Disposition	Normal (N=13) n (%)	Mild (N=7) n (%)	Moderate (N=8) n (%)	Severe (N=6) n (%)	All Subjects (N=34) n (%)
Enrolled	13 (100.0)	7 (100.0)	8 (100.0)	6 (100.0)	34 (100.0)
Completed	13 (100.0)	7 (100.0)	8 (100.0)	6 (100.0)	34 (100.0)

Normal = Non hepatic impaired, Mild = Child-Pugh class A, Moderate = Child-Pugh class B, Severe = Child-Pugh class C.

Demographic and Background Characteristics

Demographic characteristics by hepatic impairment status based on Child-Pugh classification at baseline (FAS)

Demographic Variables	Normal (N=13)	Mild (N=7)	Moderate (N=8)	Severe (N=6)	All Subjects (N=34)
Age (years)					
n	13	7	8	6	34
Mean	39.0	47.3	50.8	48.7	45.2
SD	7.30	6.34	8.38	11.64	9.37
Sex, n (%)					
Male	10 (76.9)	7 (100.0)	5 (62.5)	5 (83.3)	27 (79.4)
Female	3 (23.1)	0 (0.0)	3 (37.5)	1 (16.7)	7 (20.6)
Race, n (%)					
Caucasian	10 (76.9)	7 (100.0)	8 (100.0)	6 (100.0)	31 (91.2)
Black	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Asian	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.9)
Ethnicity, n (%)					
Chinese	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.9)
Mixed Ethnicity	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Other	10 (76.9)	7 (100.0)	8 (100.0)	6 (100.0)	31 (91.2)
Weight (kg)					
n	13	7	8	6	34
Mean	80.99	80.50	74.71	69.48	77.38
SD	13.033	6.143	16.164	8.034	12.414
Height (cm)					
n	13	7	8	6	34
Mean	175.4	179.3	168.6	171.7	173.9
SD	8.12	8.12	10.29	10.11	9.41
BMI (kg/m^2)					
n	13	7	8	6	34
Mean	26.22	25.19	26.29	23.93	25.62
SD	3.058	3.170	4.875	5.193	3.894
BSA (m^2)					

n	13	7	8	6	34
Mean	1.99	2.01	1.89	1.82	1.94
SD	0.210	0.090	0.217	0.098	0.186

Normal = Non hepatic impaired, Mild = Child-Pugh class A, Moderate = Child-Pugh class B, Severe = Child-Pugh class C.

Body mass index (BMI) = weight (kg) / height $(m)^2$.

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

Primary Objective Result(s)

Summary of primary PK parameters for everolimus by hepatic impairment status, based on Child-Pugh classification at baseline (PK Set)

Treatment	Statistics	C_{max} (ng/mL)	$AUC_{(0\text{-}inf)}$ (hr*ng/mL)	$AUC_{(0\text{-}tlast)}$ (hr*ng/mL)	T_{max} (hr)	Cl/F (L/hr)	Cl_F/BSA (L/[hr*m**2])
Normal	n	13	13	13	13	13	13
	Mean (SD)	33.838 (12.7505)	317.437 (55.4377)	298.494 (53.5401)		32.564 (6.7437)	16.368 (3.0759)
	CV% mean	37.68	17.46	17.94		20.71	18.79
	Geo-mean	31.534	312.513	293.527		31.999	16.116
	CV% geo-mean	41.72	19.11	19.91		19.11	18.24
	Median	31.200	323.414	304.781	1.000	30.920	15.454
	[Min; Max]	[15.90; 55.10]	[202.25; 395.13]	[186.18; 372.86]	[1.00; 4.00]	[25.31; 49.45]	[12.73; 21.90]
Mild	n	7	7	7	7	7	7
	Mean (SD)	31.343 (5.5734)	642.421 (308.4698)	565.458 (235.8944)		19.488 (10.3721)	9.637 (4.9031)
	CV% mean	17.78	48.02	41.72		53.22	50.88
	Geo-mean	30.920	576.512	518.716		17.346	8.639
	CV% geo-mean	17.94	55.44	49.34		55.44	53.78
	Median	32.400	752.258	614.975	1.500	13.293	6.816
	[Min; Max]	[24.90; 39.80]	[265.97; 1161.11]	[248.46; 904.84]	[1.00; 4.00]	[8.61; 37.60]	[4.42; 17.80]
Moderate	n	8	8	8	8	8	8
	Mean (SD)	48.888 (12.0662)	1029.543 (330.3592)	892.187 (261.3682)		10.625 (3.4193)	5.689 (1.9120)
	CV% mean	24.68	32.09	29.30		32.18	33.61
	Geo-mean	47.449	984.442	859.710		10.158	5.437
	CV% geo-mean	27.35	32.98	29.74		32.98	32.30
	Median	54.100	1028.858	866.992	1.000	9.822	4.847
	[Min; Max]	[30.80; 61.20]	[628.44; 1651.78]	[588.59; 1364.58]	[0.50; 3.00]	[6.05; 15.91]	[3.60; 8.63]
Severe	n	6	6	6	6	6	6
	Mean (SD)	34.600 (16.7216)	1296.509 (747.1444)	990.476 (485.4542)		9.966 (5.2465)	5.488 (2.9076)
	CV% mean	48.33	57.63	49.01		52.65	52.98

	Geo-mean	31.656	1136.088	899.560		8.802	4.825
	CV% geo-mean	47.24	60.79	50.77		60.79	62.64
	Median	25.800	1106.908	888.877	2.250	9.092	5.271
	[Min; Max]	[21.50; 57.00]	[549.61; 2588.61]	[484.82; 1814.96]	[0.50; 4.00]	[3.86; 18.20]	[2.07; 10.12]

Normal = non hepatic impaired, Mild = Child-Pugh class A, Moderate = Child-Pugh class B, Severe = Child-Pugh class C.

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

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

Summary of secondary PK parameters for everolimus by hepatic impairment status, based on Child-Pugh classification at baseline (PK Set)

Treatment	Statistics	$T_{1/2}$ (hr)	Lz (1/hr)	V_F (L)
Normal	n	13	13	13
	Mean (SD)	35.173 (8.9506)	0.021 (0.0053)	1612.575 (345.9592)
	CV% mean	25.45	25.10	21.45
	Geo-mean	34.176	0.020	1577.708
	CV% geo-mean	25.24	25.56	22.22
	Median	33.615	0.021	1519.109
	[Min; Max]	[21.96; 54.57]	[0.01; 0.03]	[1096.54; 2052.46]
Mild	n	7	7	7
	Mean (SD)	51.703 (18.1514)	0.015 (0.0043)	1288.730 (429.3818)
	CV% mean	35.11	29.61	33.32
	Geo-mean	49.327	0.014	1234.381
	CV% geo-mean	33.04	34.08	31.83
	Median	45.150	0.015	1341.873
	[Min; Max]	[34.56; 83.79]	[0.01; 0.02]	[860.91; 2124.04]
Moderate	n	8	8	8
	Mean (SD)	59.102 (9.4796)	0.012 (0.0024)	876.835 (204.3649)
	CV% mean	16.04	20.35	23.31
	Geo-mean	58.367	0.012	855.368
	CV% geo-mean	17.51	18.81	24.43
	Median	61.229	0.011	903.435
	[Min; Max]	[41.23; 68.18]	[0.01; 0.02]	[595.46; 1179.35]
Severe	n	6	6	6
	Mean (SD)	77.698 (13.7128)	0.009 (0.0015)	1038.311 (400.4304)
	CV% mean	17.65	16.06	38.57
	Geo-mean	76.740	0.009	974.504
	CV% geo-mean	17.20	16.80	40.96
	Median	73.302	0.010	959.887
	[Min; Max]	[62.29; 99.86]	[0.01; 0.01]	[556.56; 1635.07]

Normal = non hepatic impaired, Mild = Child-Pugh class A, Moderate = Child-Pugh class B, Severe = Child-Pugh class C.

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

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

Summary statistics of primary PK parameters for everolimus by hepatic impairment status, based on Child-Pugh classification on Day 8 (PK Set)

Treatment	Statistics	C_{max} (ng/mL)	$AUC_{(0\text{-}inf)}$ (hr*ng/mL)	$AUC_{(0\text{-}tlast)}$ (hr*ng/mL)	T_{max} (hr)	Cl/F (L/hr)	Cl_F/BSA (L/[hr*m**2])
Normal	n	13	13	13	13	13	13
	Mean (SD)	33.838 (12.7505)	317.437 (55.4377)	298.494 (53.5401)		32.564 (6.7437)	16.368 (3.0759)
	CV% mean	37.68	17.46	17.94		20.71	18.79
	Geo-mean	31.534	312.513	293.527		31.999	16.116
	CV% geo-mean	41.72	19.11	19.91		19.11	18.24
	Median	31.200	323.414	304.781	1.000	30.920	15.454
	[Min; Max]	[15.90; 55.10]	[202.25; 395.13]	[186.18; 372.86]	[1.00; 4.00]	[25.31; 49.45]	[12.73; 21.90]
Mild	n	6	6	6	6	6	6
	Mean (SD)	36.950 (13.1500)	538.852 (211.5382)	491.613 (183.2747)		21.643 (9.7725)	10.882 (4.4300)
	CV% mean	35.59	39.26	37.28		45.15	40.71
	Geo-mean	35.273	500.764	460.391		19.970	10.159
	CV% geo-mean	33.31	45.46	42.79		45.46	42.35
	Median	34.750	550.188	512.233	1.500	18.904	10.309
	[Min; Max]	[24.90; 61.20]	[265.97; 756.62]	[248.46; 723.33]	[0.50; 4.00]	[13.22; 37.60]	[6.42; 17.80]
Moderate	n	9	9	9	9	9	9
	Mean (SD)	43.200 (12.9878)	1055.575 (297.7875)	905.115 (231.0626)		10.174 (2.9480)	5.298 (1.4871)
	CV% mean	30.06	28.21	25.53		28.98	28.07
	Geo-mean	41.441	1018.952	880.049		9.814	5.138
	CV% geo-mean	31.57	28.94	25.45		28.94	25.96
	Median	37.100	1133.961	904.836	1.500	8.819	4.679
	[Min; Max]	[26.50; 59.30]	[628.44; 1651.78]	[588.59; 1364.58]	[1.00; 3.00]	[6.05; 15.91]	[3.60; 8.59]
Severe	n	6	6	6	6	6	6
	Mean (SD)	34.600 (16.7216)	1296.509 (747.1444)	990.476 (485.4542)		9.966 (5.2465)	5.488 (2.9076)
	CV% mean	48.33	57.63	49.01		52.65	52.98
	Geo-mean	31.656	1136.088	899.560		8.802	4.825
	CV% geo-mean	47.24	60.79	50.77		60.79	62.64
	Median	25.800	1106.908	888.877	2.250	9.092	5.271
	[Min; Max]	[21.50; 57.00]	[549.61; 2588.61]	[484.82; 1814.96]	[0.50; 4.00]	[3.86; 18.20]	[2.07; 10.12]

Normal = non hepatic impaired, Mild = Child-Pugh class A, Moderate = Child-Pugh class B, Severe = Child-Pugh class C.

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

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

Summary of statistical analysis of primary PK parameters for everolimus by hepatic impairment status, based on Child-Pugh classification on Day 8 (PK Set)

					Treatment Comparison		
						90% CI	
PK Parameter (unit)	**Treatment**	**n ***	**Adjusted Geo-mean**	**Comparison**	**Geo-mean Ratio**	**Lower**	**Upper**
$AUC_{(0\text{-}inf)}$	Normal	13	312.51				
(ng*hr/mL)	Mild	6	500.76	Mild:Normal	1.60	1.20	2.14
	Moderate	9	1018.95	Moderate:Normal	3.26	2.53	4.21
	Severe	6	1136.09	Severe:Normal	3.64	2.72	4.86
$AUC_{(0\text{-}tlast)}$	Normal	13	293.53				
(ng*hr/mL)	Mild	6	460.39	Mild:Normal	1.57	1.21	2.04
	Moderate	9	880.05	Moderate:Normal	3.00	2.38	3.78
	Severe	6	899.56	Severe:Normal	3.06	2.36	3.99
Cl/F	Normal	13	32.00				
(L/hr)	Mild	6	19.97	Mild:Normal	0.62	0.47	0.83
	Moderate	9	9.81	Moderate:Normal	0.31	0.24	0.40
	Severe	6	8.80	Severe:Normal	0.28	0.21	0.37
Cl_F/BSA	Normal	13	16.12				
(L/(hr*m2))**	Mild	6	10.16	Mild:Normal	0.63	0.48	0.84
	Moderate	9	5.14	Moderate:Normal	0.32	0.25	0.41
	Severe	6	4.82	Severe:Normal	0.30	0.23	0.40
C_{max}	Normal	13	31.53				
(ng/mL)	Mild	6	35.27	Mild:Normal	1.12	0.82	1.53
	Moderate	9	41.44	Moderate:Normal	1.31	1.00	1.73
	Severe	6	31.66	Severe:Normal	1.00	0.73	1.37
T_{max}	Normal	13	1.00				
(hr)	Mild	6	1.50	Mild-Normal	0	-0.50	0.50
	Moderate	9	1.50	Moderate-Normal	0	-0.50	0.50
	Severe	6	2.30	Severe-Normal	1.00	-0.50	1.50

n* = number of subjects with non-missing values

Model is a linear mixed effects model of the log-transformed PK parameters including hepatic impairment group (Child-Pugh A, B and C and normal hepatic function) as a fixed effect.

For T_{max}, median is presented under 'Adjusted Geo-mean', Hodges-Lehmann estimate under 'Geo-mean Ratio', and distribution free CI under 90% CI.

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class, preferred term and group (Safety Set)

Primary system organ class Preferred term	Normal (N=13) n (%)	Mild (N=7) n (%)	Moderate (N=8) n (%)	Severe (N=6) n (%)
Any primary system organ class				
Total	1 (7.7)	1 (14.3)	3 (37.5)	2 (33.3)
Immune system disorders				
Total	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Psychiatric disorders				
Total	0 (0.0)	0 (0.0)	1 (12.5)	1 (16.7)
Insomnia	0 (0.0)	0 (0.0)	1 (12.5)	1 (16.7)
Investigations				
Total	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
Biopsy	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
Nervous system disorders				
Total	0 (0.0)	1 (14.3)	1 (12.5)	0 (0.0)
Dizziness	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
Headache	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders				
Total	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)

Normal = non hepatic impaired, Mild = Child-Pugh class A, Moderate = Child-Pugh class B, Severe = Child-Pugh class C.

Primary system organ classes are presented alphabetically; Preferred terms are sorted within primary system organ class by descending order of frequencies, using severe as the reference group.

A subject with multiple occurrences of an AE under one group is counted only once in the AE category for that group.

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

Serious Adverse Events and Deaths

One SAE was reported in the moderate group. This was a pre-scheduled procedure of liver biopsy that was not study drug related. There were no deaths.

There were no clinically relevant changes in hematology variables or coagulation profile, hepatic or renal function tests, or common biochemistry tests.

Other Relevant Findings

- A significant positive correlation of $AUC_{(0\text{-}inf)}$ with bilirubin level and INR was observed irrespective of the Child-Pugh scores. Similarly, a significant negative correlation with albumin was also noted. However use of these parameters alone resulted in some cases of either under dosing or over dosing in some subjects, thereby warranting the use of Child-Pugh scores as the most conservative means of dose reduction, in hepatic impaired subjects.

- It is recommended to use Child-Pugh status as a guide to implement dosing administration adjustments.
- Everolimus at a starting dose of 7.5 mg daily is recommended for subjects with mild hepatic impairment (Child-Pugh A), and a dose of 2.5 mg daily is recommended for subjects with moderate hepatic impairment (Child-Pugh B).
- Everolimus is not recommended for subjects with severe hepatic impairment (Child-Pugh C) unless it is in the best interest of the subject. In the absence of other treatment options, everolimus at a dose of 2.5 mg daily may be administered and must not be exceeded.

Date of Clinical Trial Report

15 Mar 2011

Date Inclusion on Novartis Clinical Trial Results Database

23 May 2011

Date of Latest Update