Sponsor

Novartis

Generic Drug Name

Fingolimod

Therapeutic Area of Trial

Neuroscience

Approved Indication

Investigational drug

Study Number

CFTY720D2108

Title

An open-label, single-dose, parallel-group study to compare the pharmacokinetics of FTY720 and metabolites in subjects with severe renal impairment with that in matched healthy control subjects

Phase of Development

Phase II

Study Start/End Dates

18 Jul 2008 to 25 Aug 2008

Study Design/Methodology

An open-label, single-dose, parallel-group study to compare the pharmacokinetics of FTY720 and its metabolites in patients with severe renal insufficiency and in matched healthy volunteers. Nine patients with severe renal impairment and nine healthy volunteers matching by ethnicity, smoking status, gender, age (±5 years), and body weight (± 10%) were administered a single dose of FTY720 1.25 mg capsule, immediately after a modest breakfast. Subjects/patients were released from the study centre on the morning of Day 4, and returned on days 6, 10, 14 and 21 (end of study visit) for PK, PD and safety assessments.

Centres

Two centers in Russia

Publication

None

Objectives

Primary objective

- To assess the influence of renal function on the pharmacokinetics of FTY720 and FTY720-P after single oral administration of 1.25 mg FTY720 capsule in healthy subjects and in severe renal impaired patients.

Secondary objectives

- To assess the safety and tolerability of FTY720 in healthy subjects and in severe renal impaired patients.
- To assess the influence of renal function on the pharmacokinetics of FTY720 metabolites M2 and M3.

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

Oral, single dose of FTY720 1.25 mg / FMI hard gelatin capsule, batch number H378BD.

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

NA

Criteria for Evaluation

Primary variables

Pharmacology: blood concentrations of FTY720, FTY720-P, M2 and M3 by LC/MS/MS-method with lower limit of quantification (LLOQ) of 0.08 ng/mL for FTY720 and 0.1 ng/mL for FTY720-P, M2 and M3. The pharmacokinetic parameters for FTY720, FTY720-P, M2 and M3 were determined using non-compartmental method(s) using WinNonlin Pro (Version 5.2).

Secondary variables

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), pregnancies, blood laboratory tests (hematology, blood chemistry and urinalysis) performed at study center / central laboratory, regular assessments of vital signs, physical condition, body weight, 12-lead ECGs and recording of all concomitant medications/non-drug therapies were obtained.

Statistical Methods

The demographic variables were summarized by group (severe impaired subjects (test) and control subjects (reference).

Adverse events incidence was calculated by System Organ Class and group; most frequent preferred terms (with incidence of at least 10% in either group), serious AEs, deaths, and discontinuation due to SAEs were also tabulated by group.

Statistical analysis was performed for the PK parameters $AUC_{(0\text{-}tz),b}$, AUC_b, $AUC_{(0\text{-}72),b}$, and $C_{max,b}$. A linear model was fitted to the log-transformed observations in order to compare the severe impaired subjects (test) to the control subjects (reference). This model included the overall mean and group (test or reference). Estimates for the difference between the two groups including a 90% confidence interval were obtained based upon the log-transformed observations. These estimates and confidence intervals were then “back-transformed” to give estimates of the ratios of the two groups and associated 90% confidence intervals. This analysis was performed for each analyte.

The other PK parameters were summarized by group by means of descriptive statistics.

The plasma protein binding was summarized by group, by means of descriptive statistics and compared using an unpaired Student t-test.

Study Population: Inclusion/Exclusion Criteria and Demographics

All Subjects/Patients

1. Male and female subjects/patients 18-65 years of age, weighing at least 50 kg, and with a body mass index (BMI) within the range of 18 to 32 kg/m^2.

2. Male subjects using two acceptable methods of contraception.

Healthy Subjects

1. In good health, determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.
2. Female subjects: of non child bearing potential, history of hysterectomy, bilateral oophorectomy (ovariectomy), bilateral tubal ligation, or post-menopausal.
3. Calculated glomerular filtration rate (GFR) by Cockcroft-Gault Equation ≥80 mL/min.
4. Vital signs (after 3 minutes supine) within ranges: oral body temperature 35.0-37.5 °C, systolic blood pressure 90-140 mmHg, diastolic blood pressure 45-90 mmHg, pulse rate 50 - 90 BPM

Severe Renal Impaired Patients

1. Patients not on dialysis with severe renal failure with a CLcr < 30 mL/min as determined by Cockcroft-Gault Equation
2. Renal function should have been stable within the 3 months prior to study start.
3. Female subjects of non-child-bearing potential, history of hysterectomy, bilateral oophorectomy (ovariectomy), bilateral tubal ligation, or post-menopausal. Agreeable to one of the following if of childbearing potential: an appropriate form of contraception (e.g. oral contraceptive, bilateral tubal ligation, intra-uterine device (IUD) (excluding progesterone-coated), or barrier methods (e.g. condom or occlusive cap (diaphragm or cervical vault/caps) from at least the commencement of their last normal period prior to the first dose of study medication and to continue for at least 6 weeks after the last dose of study medication. Vasectomized partner, who is sterile prior to the female subject's entry and is the sole sexual partner for that female.
4. Patients with diabetes and/or hypertension in otherwise in good health, however patients with diabetes must have had clinical evidence of gastropathy or enteropathy.
5. Vital signs (after 3 minutes supine) within ranges: oral body temperature 35.0-37.5 °C. systolic blood pressure 100-180 mm Hg, diastolic blood pressure 50-100 mm Hg, pulse rate 60-100 BPM
6. Patients were not allowed to have undergone hemodialysis or peritoneal dialysis in the last 6 months.

Exclusion criteria

All Subjects/Patients

1. Participation in any clinical investigation within 4 weeks prior to dosing, donation or loss of 400 mL or more of blood within eight (8) weeks prior to initial dosing, or longer for both, if required by local regulation.
2. History of multiple and recurring allergies or allergy to the investigational compound/compound class being used in the study.
3. History of retinal macular edema.
4. History of any significant cardiovascular events such as myocardial infarction, valvu-

lar disease, angina, ischemic heart disease, dilated cardiomyopathy, dysrhythmia.

5. Past medical history of clinically significant ECG abnormalities or a family history of a prolonged QT-interval syndrome. Abnormal ECG defined as QTcB (corrected QT interval, by Bazett's formula) for females > 470 msec, QTcB for males >450 msec.
7. Any surgical or medical condition which may have significantly altered the absorption, distribution, metabolism, or excretion of drugs, or, which may have jeopardize the subject in participation in the study. Determined by medical history and/or clinical or laboratory evidence of any of the following: Inflammatory bowel syndrome; Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection; Pancreatic injury or pancreatitis; Liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), γ-GGT, alkaline phosphatase, or serum bilirubin. The following criteria as a guide:
    - SGPT (ALT) exceeding 1.5 times the upper normal range before inclusion, γ-GGT, AST and alkaline phosphatase exceeding twice the upper limit of normal, Serum bilirubin exceeding the value of 27 µmol/L (1.6 mg/dL), evidence of urinary obstruction or difficulty in voiding at screening.
8. History of immunocompromise, including a positive HIV (ELISA and Western blot) test result, positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result
9. History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays.

Healthy Subjects

1. Use of any prescription drugs (except hormone replacement therapy) within four (4) weeks prior dosing, or over-the-counter (OTC) medication (vitamins, herbal supplements, dietary supplements) within two (2) weeks prior to dosing.
2. Significant illness (deemed by the Investigator) within two (2) weeks prior to initial dosing.

Severe Renal Impaired Patients

1. Use of any highly potent CYP3A4 inhibitor (e.g. erythromycin, ketoconazole, itraconazole), beta blocker therapy or herbal supplements within 2 weeks prior to dosing.

Number of Subjects

	Healthy subjects FTY720 (1.25 mg)	**Renal impaired FTY720 (1.25 mg)**
Planned N	9	9
Randomised n	not applicable	not applicable
Intent-to-treat population (ITT) n (%)	9 (100%)	9 (100%)
Completed n (%)	9 (100%)	9 (100%)
Withdrawn n (%)	0 (0%)	0 (0%)
Withdrawn due to adverse events n (%)	0 (0%)	0 (0%)
Withdrawn due to lack of efficacy n (%)	not applicable	not applicable
Withdrawn for other reasons n (%)	0 (0%)	0 (0%)

Demographic and Background Characteristics

Demographic variable		Renal impaired N=9	Healthy controls N=9	All subjects N=18
Age (years)	Mean (SD)	47.9 (10.01)	47.1 (10.23)	47.5 (9.82)
Height (cm)	Mean (SD)	164.9 (8.78)	171.2 (9.19)	168.1 (9.31)
Weight (kg)	Mean (SD)	67.58 (16.764)	69.33 (16.416)	68.46 (16.120)
Body mass index (kg/m^2)	Mean (SD)	24.5 (3.73)	23.4 (3.36)	24.0 (3.49)
Sex	Male	4 (44.4 %)	4 (44.4 %)	8 (44.4 %)
	Female	5 (55.6 %)	5 (55.6 %)	10 (55.6 %)
Predominant race	Caucasian	9 (100 %)	9 (100 %)	18 (100 %)
Serum creatinine (μmol/L)	Mean (SD)	477.9 (172.33)	68.6 (7.20)	-
Glomerular filtration rate according to Cockcroft-Gault (mL/min)	Mean (SD)	16.24 (7.112)	100.94 (16.836)	-

Primary Objective Results

Pharmacokinetics in renal impaired patients and in matched healthy volunteers

Geometric mean ratio (test/reference) and 90% confidence intervals for FTY720 PK parameters in blood

	Adjusted geo-mean*		Geo-mean ratio*		
Parameter (Unit)	**Impaired**	**Control**	**Estimate**	**Lower 90% CL**	**Upper 90% CL**
$C_{max,b}$ (ng/mL)	0.844	0.639	1.32	1.06	1.65
$AUC_{(0-tz),b}$ (h*ng/mL)	91.226	61.576	1.48	0.94	2.33
AUC_b (h*ng/mL)	109.440	76.723	1.43	0.94	2.18
$AUC_{(0-72),b}$ (h*ng/mL)	45.638	34.379	1.33	1.04	1.69

* back-transformed from log scale; geo-mean=geometric mean.

Geometric mean ratio (test/reference) and 90% confidence intervals for FTY720-P PK parameters in blood

	Adjusted geo-mean*		Geo-mean ratio*		
Parameter (Unit)	**Impaired**	**Control**	**Estimate**	**Lower 90% CL**	**Upper 90% CL**

PK parameters	**FTY720**		**FTY720-P**	
	Renal impaired	**Healthy subjects**	**Renal impaired**	**Healthy subjects**
$C_{max,b}$ # (ng/mL)	0.878 ± 0.256 [0.844; 31]	0.653 ± 0.138 [0.639; 24]	1.13 ± 0.293 [1.097; 25]	0.904 ± 0.229 [0.876; 28]
$AUC_{(0-72),b}$ # (ng/mL.h)	47.7 ± 13.9 [45.6; 34]	35.3 ± 8.00 [34.4; 26]	30.5 ± 6.801 [29.7; 26]	27.3 ± 6.12 [26.6; 25]
$AUC_{(0-tz),b}$ # (ng/mL.h)	109.7 ± 72.4 [91.2; 72]	67.4 ± 33.6 [61.6; 46]	42.9 ± 24.5 [37.7; 58]	37.1 ± 18.2 [33.9; 47]
AUC_b # (ng/mL.h)	131 ± 90.7 [109; 68]	82.3 ± 36.9 [76.7; 39]	75.5 ± 33.6 + [70.2; 44]	65.9 ± 30.6 + [61.7; 39]
$t_{1/2}$ # (h)	94 ± 53 [85; 45]	85 ± 25 [83; 24]	95.1 ± 50.4 + [85.1; 56]	100.7 ± 46.1 + [94.4; 39]

#: arithmetic mean ± standard deviation [geometric mean, % geometric mean coefficient of variation]; *: median (minimum-maximum); NA: Not applicable as FTY720-P not measured in the urine;

+: n=5

a: no subject with concentrations >LLOQ; b: statistics not reported as only 1 subject with concentrations >LLOQ

$C_{max,b}$ (ng/mL)	1.097	0.876	1.25	1.01	1.56
$AUC_{(0-tz),b}$ (h*ng/mL)	37.661	33.923	1.11	0.74	1.67
AUC_b (h*ng/mL)	70.198	61.695	1.14	0.71	1.82
$AUC_{(0-72),b}$ (h*ng/mL)	29.658	26.572	1.12	0.91	1.37

* back-transformed from log scale; geo-mean=geometric mean.

Secondary Objective Results

M2 and M3 pharmacokinetics in renal impaired patients and in matched healthy volunteers after a 1.25 mg dose (n=9 in each group)

PK parameters	M2		M3	
	Renal impaired	Healthy subjects	Renal impaired	Healthy subjects
$C_{max,b}$ # (ng/mL)	0.303 ± 0.125 [0.279; 48]	b	5.76 ± 3.70 [5.082; 52]	0.676 ± 0.231 [0.631; 45]
$AUC_{(0-72),b}$ # (ng/mL.h)	11.1 ± 5.72 [9.43; 76]	b	290 ± 142 [267; 42]	31.4 ± 11.7 [29.1; 46]
$AUC_{(0-tz),b}$ # (ng/mL.h)	11.9 ± 8.49 [9.03; 103]	b	1092 ± 699 [906; 72]	46.2 ± 21.8 [40.9; 61]
AUC_b # (ng/mL.h)	a	b	1230 ± 802 [1003; 79]	76.4 ± 20.1 + [74.0; 29]
$t_{1/2}$ # (h)	a	b	116 ± 63 [104; 48]	95 ± 54 + [85; 53]

#: arithmetic mean ± standard deviation [geometric mean, % geometric mean coefficient of variation];
*: median (minimum-maximum);
+: n=6
a: Parameter not reliably estimated, b: no subject with concentrations >LLOQ

Geometric mean ratio (test/reference) and 90% confidence intervals for M3 PK parameters in blood

	Adjusted geo-mean*		Geo-mean ratio*		
Parameter (Unit)	Impaired	Control	Estimate	Lower 90% CL	Upper 90% CL
$C_{max,b}$ (ng/mL)	5.082	0.631	8.05	5.53	11.72
$AUC_{(0-tz),b}$ (h*ng/mL)	905.959	40.928	22.14	13.43	36.49
AUC_b (h*ng/mL)	1002.995	73.979	13.56	7.95	23.14
$AUC_{(0-72),b}$ (h*ng/mL)	267.001	29.060	9.19	6.50	12.99

* back-transformed from log scale; geo-mean=geometric mean.

The effect of severe renal impairment on the blood pharmacokinetics of M2 could not be assessed, as all M2 blood concentrations were below LLOQ in the healthy volunteers.

Adverse Events by System Organ Class

		Renal impaired N=9		Healthy controls N=9		Total N=18	
System Organ Class (SOC)	**Preferred term**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
- Any SOC		9	(100)	9	(100)	18	(100)
Cardiac disorders	- Total	3	(33.3)	6	(66.7)	9	(50.0)
	Bradycardia	3	(33.3)	6	(66.7)	9	(50.0)
	Sinoatrial block	1	(11.1)	0	(0.0)	1	(5.6)
Investigations	- Total	9	(100)	9	(100)	18	(100)
	Alanine aminotransferase increased	1	(11.1)	0	(0.0)	1	(5.6)
	Electrocardiogram QT prolonged	3	(33.3)	0	(0.0)	3	(16.7)
	Lymphocyte count decreased	9	(100)	9	(100)	18	(100)
Nervous system disorders	- Total	1	(11.1)	1	(11.1)	2	(11.1)
	Headache	1	(11.1)	1	(11.1)	2	(11.1)

Arranged alphabetically by system organ class

Most frequent AEs - preferred terms with incidence of at least 10% in either FTY720 group N (%)

	Renal impaired FTY720 (1.25mg)	Healthy subjects FTY720 (1.25mg)
Decreased lymphocyte count	9 (100)	9 (100)
Bradycardia	3 (33.3)	6 (66.7)
Electrocardiogram QT prolonged	3 (33.3)	0 (0.0)
Headache	1 (11.1)	1 (11.1)
Sinoatrial block	1 (11.1)	0 (0.0)
Alanine Aminotransferase elevated	1 (11.1)	0 (0.0)

Serious Adverse Events and Deaths

	Renal impaired FTY720 (1.25mg)	Healthy subjects FTY720 (1.25mg)
No. (%) of subjects studied	9 (100)	9 (100)
No. (%) of subjects with AE(s)	9 (100)	9 (100)
Number (%) of subjects with serious or other significant events	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)
SAE(s)	0 (0.0)	0 (0.0)
Discontinued due to SAE(s)	0 (0.0)	0 (0.0)

Other Relevant Findings

None

Date of Clinical Trial Report

05 May 2009

Date Inclusion on Novartis Clinical Trial Results Database

10 Sept 2009

Date of Latest Update

01 Sept 2009