Sponsor

Novartis

Generic Drug Name

FTY720/Fingolimod

Therapeutic Area of Trial

Multiple Sclerosis

Approved Indication

Investigational

Study Number

CFTY720D2102

Title

A double-blind, randomized, placebo-controlled, parallel, time-lagged, ascending, multi-centre, multiple-dose study to measure the magnitude and time course of the effect of FTY720 on FEV1 and other pulmonary function tests (FVC, FEF25-75%, and FEV1/FVC) in patients with moderate asthma.

Phase of Development

Phase II

Study Start/End Dates

18 Sep 2008 to 25 Feb 2009

Study Design/Methodology

This was a randomized, double-blind, placebo-controlled, parallel, time-lagged, ascending, multiple oral dose study in patients with moderate asthma. Patients were divided into 3 dosing cohorts of 12 patients each. In each cohort, the 12 patients were randomized to FTY720 (0.5mg, 1.25mg, and 2.5mg in cohorts 1, 2, and 3 respectively) or placebo in a 3:1 ratio resulting in 9 patients treated with FTY720 at each dose level and 9 patients treated with placebo.

The study consisted of a screening period of between 12 and 26 days, baseline and a 10 day treatment period followed by a study completion evaluation (performed 1-7 days after the last dose).

Two screening visits were performed, the initial Screening visit and a second visit at Day -7 (+/- 1 day). The initial screening visit (Visit 1) was used to start pulmonary function test (PFT) monitoring to assess eligibility for the study and to obtain relevant background information and informed consent. The PFT was performed at a clock time similar to the 6-hour post-dose timepoint on Day 1. On Day -7 a PFT was again performed at the specified time. Short-acting β2 agonist use prior to treatment with study medication was also recorded in this 14 day period.

Patients returned to the clinic one or 2 days prior to dosing for baseline assessments. PFT profiling was assessed at 7 time points during the visit and routine baseline evaluations were performed. On Day 1, patients were randomized in a 3:1 ratio to FTY720 or placebo and PFT profiling was assessed at 8 time points (namely pre-dose, then at 1, 2, 3, 4, 5, 6 and 12 hours post-dose). PFT assessments were also performed on Days 2, 3, 7 (all single time points assessed at approximately the same clock time as the 6 hours post-dose PFT on Day 1) and Day 10 (7 time points, namely pre-dose and then at 1, 2, 3, 4, 5 and 6 hours post-dose). On each of the days when PFT assessments were performed, a reversibility test followed the last PFT assessment of the day. Short-acting β2 agonist use was also recorded throughout the treatment period up to and including Day 11 (24hours post last dose).

Blood samples were collected on Day 1 at pre-dose and at 1, 2, 4, 6, 8, 12, 16, and 24h post-dose, on Days 2, 3 and 7 at 6 hours post-dose and on Day 10 at pre-dose and at 1, 2, 4, and 6h post-dose.

Safety assessments included physical examinations, ECGs, vital signs, spirometry assessments, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis), adverse event and serious adverse event monitoring.

Only one half of each treatment cohort, a maximum of 6 patients, was allowed to start treatment on any given day for safety reasons. At least 1 day (24 hours) separated the initial dosing of the first group of patients from the dosing of the second group (and at least 1 further day separated the second group from any subsequent groups required to complete each cohort). The study was time-lagged to allow the sponsor and investigator to review safety data prior to dose escalation.

Patients had access to rescue medication on an ongoing basis throughout the study with the exception that they were required to withhold use within the 6 hours prior to any pulmonary function testing in order to avoid any bias to the estimation of the treatment effect.

Centres

2 centres in UK

Publication

Not Applicable

Objectives

Primary objective(s)

• To measure the magnitude and time course of the effect of FTY720 on FEV_1 and other pulmonary function tests (FVC, $FEF_{25-75\%}$, and FEV_1/FVC) in patients with moderate asthma.

• To assess the safety and tolerability of once daily dosing of FTY720 in patients with moderate asthma.

Secondary objective(s)

• To assess the effect of FTY720 with once daily dosing of 0.5 mg, 1.25 mg and 2.5 mg for 10 days on the use of short-acting β2 agonists in patients with moderate asthma.

• To assess the pharmacokinetics (PK) of FTY720 and FTY720-phosphate (FTY720-P) after administration of once daily doses of FTY720 in patients with moderate asthma

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

Oral capsules of FTY720 0.5mg, 1.25mg or 2.5mg each morning for 10 days. Patients in the 0.5mg and 1.25mg cohorts were administered 1 capsule each, those in the 2.5mg cohort 2 capsules each (2x1.25mg capsules = 2.5mg).

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

Oral capsules of FTY720 matching placebo each morning for 10 days. Patients in the 0.5mg and 1.25mg cohorts were administered 1 placebo capsule each, those in the 2.5mg cohort 2 placebo capsules each to maintain the blind.

Criteria for Evaluation

Primary variables

Pulmonary Function Tests (particularly FEV1) performed at the clinic site at Day 1 and Day 10

Secondary variables

Use of short-acting β2 agonists as recorded by site staff at clinic visits, and by the patients themselves in a diary completed whilst at home.

Safety and tolerability

Collection of all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and urinalysis and regular assessments of vital signs, physical condition and body weight.

Pharmacology

Blood samples (for analysis of FTY720 and FTY720-P) were collected on day 1 at pre-dose and at 1, 2, 4, 6, 8, 12, 16, and 24h post-dose (day 2 pre-dose), on day 2, 3 and day 7 at 6 hours post-dose, and on day 10 at pre-dose and at 1, 2, 4, and 6h post-dose.

Statistical Methods

The magnitude of the FTY720-induced bronchoconstriction was primarily assessed by the baseline-adjusted FEV_1 AUC0-6h on Day 1. This primary PD variable was defined as the ratio of the AUEC FEV_1 over the 6-hour PFT profile on Day 1 divided by the same variable at baseline (Day –1).

This primary PD variable was analyzed on the log-scale by means of a linear model adjusted for the (log-transformed) baseline FEV_1 AUC0-6h and the treatment group as fixed effects. The geometric mean baseline-adjusted FEV_1 AUC0-6h was obtained from the model for each treatment group; the geometric mean ratio between each FTY720 group and placebo was also obtained along with its 95% CI, and was back-transformed to obtain the geometric mean percent change from placebo and its 95% CI.

Note that if it appeared that a PFT assessment from the 6-hour PFT profile was done after intake of rescue SABA, the corresponding PD variable was flagged in the listings and not included in the summary and statistical analyses.

Additional PD variables were calculated: baseline-adjusted FEV_1 AUC0-6h on Day 10 and baseline-adjusted FEV_1 Emax1-6h on Days 1 and 10. The Emax variables were defined as the ratio between Day 1 (or Day 10) and Day –1 regarding the minimum from 6 assessments scheduled at 1 to 6 hours post dose. Those variables were defined for FEV_1 as well as for the other PFT parameters (FVC, $FEF_{25-75\%}$, and FEV_1/FVC) and were analyzed using the same model as for the primary PD endpoint.

The time-course of the PFT parameters was explored on Day 1 over the 12-hour profile and on Day 10 over the 6-hour profile. The percent change from time-matched baseline in FEV_1, FVC, $FEF_{25-75\%}$, and FEV_1/FVC was summarized by means of descriptive statistics at each visit/time point. The log-transformed ratio from time-match baseline was analyzed, separately at each post-baseline visit/time point, by means of a linear model adjusted for the time-matched log-transformed baseline value and the treatment group as fixed effect. For each FTY720 group, the estimate for the mean treatment difference versus placebo and its 95% CI were obtained from the model and were back-transformed to obtain the geometric mean percent change from placebo and its 95% CI. No adjustment was made to the P values for multiple testing.

The effect of FTY720 on the number of short-acting β2 agonist doses taken during the treatment period was analyzed by means of a Poisson regression model adjusted for the treatment group and for the average weekly number of short-acting β2 agonist doses during the baseline period as fixed effects. The fact that the duration of observation might differ across patients, e.g., in case of discontinuation, was accounted for by using that duration expressed in number of days (then log-transformed) as an offset of the model. For each treatment group, the mean daily number of intake and its 95% CI were derived from the model. For each FTY720 group, the ratio and corresponding percent difference versus placebo in the daily number of intake was also derived along with their 95% CIs.

The number of patients with adverse events was counted by body system and preferred term and tabulated by treatment group. A patient with multiple adverse events within a body system was only counted once towards the total of this body system.

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients were included in this study who met the following criteria:

- Male and female patients aged 18-65 years, healthy except for moderate asthma (for at least 6 months) defined as FEV_1 at screening of ≥ 60% of normal predicted FEV_1, use of a short-acting inhaled β_2-agonist (up to a maximum of 7 intakes per week) plus inhaled corticosteroid at a constant dose and a long-acting inhaled β_2 agonist at a constant dose (all medications for at least one month prior to screening)
- Pre-treatment FEV_1 within 15% of the actual screening value (litres) and ≥ 60% of normal predicted FEV_1.
- No exacerbation of asthma within 3 months
- Male subjects had to be sterile or willing to use a clinically-approved method of contraception from the time of study entry until at least 3 months after the last dose of study medication.

- All female patients must have had a negative serum pregnancy test at screening, and to have been physiologically incapable of becoming pregnant, or using acceptable methods of contraception as defined in the protocol.
- Vital signs at screening and baseline were within the following ranges:
  - oral body temperature between 35.0-37.5 °C
  - systolic blood pressure, 90-140 mm Hg
  - diastolic blood pressure, 50-90 mm Hg
  - pulse rate, 45 - 90 bpm

  When blood pressure and pulse was taken again after 3 minutes standing, there was no more than a 20 mm Hg drop in systolic or 10 mm Hg drop in diastolic blood pressure and increase in heart rate (>20 bpm) associated with clinical manifestation of postural hypotension.
- Patients weighed at least 50kg and had a body mass index (BMI) within the range of 18 to 33 kg/m^2.
- Were able to communicate well with the investigator, to understand and comply with the requirements of the study. Understood and signed the written informed consent.

Patients were excluded who met the following criteria:

- Patients who had smoked within 6 months of screening or who had a smoking history greater than 10 pack-years. Smokers were defined as any subject who reported tobacco use and/or who had a urine cotinine ≥ 500 ng/mL.
- Use of any oral or injected corticosteroid as defined in the protocol
- A history of a pulmonary disorder other than asthma.
- A respiratory tract infection within 1 month prior to screening.
- History of clinically significant drug allergy. A known hypersensitivity to the study drug or drugs similar to the study drug.
- Participated in any clinical research trial in which the patient received investigational product within three (3) months or 5 half lives, whichever was longer, prior to initial dosing (or longer if required by local regulations, and for any other limitation of participation based on local regulations).
- Donation or loss of 400 ml or more of blood within eight (8) weeks prior to initial dosing, or longer if required by local regulation.
- Significant illness within the two weeks prior to dosing.
- A past medical history of clinically significant ECG abnormalities, or a known family history (grandparents, parents, siblings) of a prolonged QT-interval syndrome, or an abnormal ECG defined as QTcB> 470 msec females; QTcB> >450 msec males.
- History of autonomic dysfunction (e.g., recurrent episodes of fainting, orthostatic hypotension, sinus arrhythmia).
- Any surgical or medical condition that in the opinion of the investigator might significantly altered the absorption, distribution, metabolism, or excretion of drugs, or which may have jeopardized the subject in case of participation in the study, as detailed in the protocol.

- History of immunodeficiency diseases, including a positive HIV test result.
- A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.

History of drug or alcohol abuse within the 12 months prior to dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening or baseline evaluations.

Number of Subjects

	FTY720 0.5mg	**FTY720 1.25mg**	**FTY720 2.5mg**	**Placebo**
Planned N	9	9	9	9
Randomised n	9	9	9	9
Completed n (%)	9	8	9	8
Withdrawn n (%)	0	1	0	1
Withdrawn due to adverse events n (%)	0	1	0	1

Demographic and Background Characteristics

	FTY720 0.5mg	**FTY720 1.25mg**	**FTY720 2.5mg**	**Placebo**
N (ITT)	9	9	9	9
Females : males	5:4	7:2	5:4	5:4
Mean age, years (SD)	43 (11.1)	38 (15.0)	37 (13.0)	38 (9.5)
Mean weight, kg (SD)	77.4 (17.12)	67.9 (7.73)	76.8 (13.38)	77.3 (11.08)
Race				
White n (%)	8 (89%)	6 (67%)	9 (100%)	8 (89%)
Black n (%)	0 (0%)	1 (11%)	0 (0%)	0 (0%)
Asian n (%)	1 (11%)	1 (11%)	0 (0%)	1 (11%)
Other n (%)	0 (0%)	1 (11%)	0 (0%)	0 (0%)

Primary Objective Result(s)

Statistical analysis of baseline adjusted/AUEC0-6h FEV1 at Day 1 and 10

Day	**Treatment**	**% change from baseline Geometric mean (95% CI)**	**% change from placebo Geometric mean (95% CI)**	**P-value**
1	Placebo	-4.24 (-6.79, -1.62)		
	FTY720 0.5mg	-3.41 (-5.99, -0.76)	0.87 (-2.93, 4.81)	0.65
	FTY720 1.25mg	-5.03 (-7.56, -2.42)	-8.82 (-4.55, 3.05)	0.66
	FTY720 2.5mg	-4.97 (-7.52, -2.35)	-0.76 (-4.48, 3.09)	0.68
10	Placebo	-4.25 (-7.49, -0.90)		
	FTY720 0.5mg	-2.96 (-6.26, 0.46)	-1.35 (-3.49, 6.44)	0.58
	FTY720 1.25mg	-10.10 (-13.33, -6.75)	-6.11 (-10.72, -1.25)	0.016
	FTY720 2.5mg	-7.53 (-10.69, -4.27)	-3.43 (-8.02, 1.40)	0.15

Secondary Objective Result(s)

Mean daily number of uses of rescue medication

	FTY720 0.5mg	FTY720 1.25mg	FTY720 2.5mg	Placebo
Baseline mean (SD)	0.081 (0.145)	0.098 (0.136)	0.053 (0.088)	0.219 (0.35)
On treatment mean (SD)	0.100 (0.229)	0.311 (0.352)	0.167 (0.26)	0.133 (0.218)
Change from baseline mean (SD)	0.019 (0.175)	0.214 (0.368)	0.113 (0.182)	-0.086 (0.185)

Safety Results

Adverse Events by System Organ Class

	FTY720 0.5mg N (%)	FTY720 1.25mg N (%)	FTY720 2.5mg N (%)	Placebo N (%)
Patients studied				
Randomized patients	N=9	N=9	N=9	N=9
Patients with AEs	5 (56)	9 (100)	7 (78)	3 (33)
Drug-related AEs by primary system organ class				
Nervous system disorders	1 (11)	4 (44)	3 (33)	2 (22)
Respiratory, thoracic and mediastinal disorders	2 (22)	3(33)	1 (11)	0
Infections and infestations	1 (11)	2 (22)	1 (11)	0
Investigations	0	1 (11)	2 (22)	0
Eye disorders	0	1 (11)	0	1 (11)
Gastrointestinal disorders	0	1 (11)	0	1 (11)
General disorders and administration site conditions	1 (11)	0	1 (11)	0
Renal and urinary disorders	1 (11)	1 (11)	0	0
Skin and subcutaneous tissue disorders	0	1 (11)	1 (11)	0
Blood and lymphatic disorders	0	0	1 (11)	0
Injury, poisoning and procedural complications	0	0	0	1 (11)
Psychiatric disorders	0	0	0	1 (11)
Reproductive system and breast disorders	0	1 (11)	0	0
Vascular disorders	0	1 (11)	0	0

Most Frequently Reported AEs Overall by Preferred Term (where total n >1) n (%)

	FTY720 0.5mg	FTY720 1.25mg	FTY720 2.5mg	Placebo
Headache	1 (11.1)	2 (22.2)	3 (33.3)	0
Dizziness	0	2 (22.2)	1 (11.1)	1 (11.1)
Asthma	1 (11.1)	2 (22.2)	0	0
Liver function test abnormal	0	1 (11.1)	2 (22.2)	0
Nasopharyngitis	1 (11.1)	1 (11.1)	1 (11.1)	0
Epistaxis	1 (11.1)	1 (11.1)	0	0

Serious Adverse Events and Deaths

There were no SAEs or deaths in the study

Other Relevant Findings

FTY720 pharmacokinetics in the three treatment groups

Day	Parameters	FTY720 0.5mg	FTY720 1.25mg	FTY720 2.5mg
1	T_{lag} (h)*	0.00 (0.00-1.05)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	T_{max} (h)*	12.05 (11.95-15.93)	12.08 (8.00-23.75)	12.05 (6.05-12.17)
	C_{max} (ng/mL)[#]	0.421 ± 0.101 [0.411; 22.5]	1.04 ± 0.2 [1.023; 19.9]	2.099 ± 0.455 [2.057; 21.4]
	AUC_{0-6h} (ng/mL.h)[#]	1.39 ± 0.498 [1.31; 36.7]	3.87 ± 1.094 [3.75; 26.7]	7.67 ± 1.35 [7.57; 17.2]
	AUC_{0-24h} (ng/mL.h)[#]	8.20 ± 2.20 [7.97; 24.5]	20.1 ± 3.66 [19.8; 18.5]	40.3 ± 7.89 [39.7; 19.1]
10	T_{max} (h)*	4.00 (1.03-6.05)	4.02 (0.98-6.05)	4.25 (4.05-6.05)
	C_{max} (ng/mL)[#]	2.52 ± 0.675 [2.45; 25.3]	5.71 ± 1.76 [5.47; 32.9]	10.4 ± 2.073 [10.15; 22.4]
	Predose (ng/mL)	2.021 ± 0.572 [1.95; 28.7]	5.051 ± 1.80 [4.75; 40.4]	8.52 ± 2.15 [8.22; 30.9]
	AUC_{0-6h} (ng/mL.h)[#]	13.9 ± 3.69 [13.5; 26.1]	32.7 ± 10.3 [31.2; 33.4]	57.9 ±12.3 [56.6; 24.7]
	Rac[#]	10.8 ± 3.77 [10.3; 33.8]	8.57 ± 2.26 [8.33; 25.9]	7.78 ± 2.20 [7.47; 31.9]

[#]: arithmetic mean ± std. dev [geometric mean; % geometric mean COV], *: median (minimum-maximum)

Date of Clinical Trial Report

5 November 2009

Date Inclusion on Novartis Clinical Trial Results Database

26 February 2010

Date of Latest Update

15 February 2010