Sponsor

Novartis

Generic Drug Name

Fluvastatin

Therapeutic Area of Trial

Dyslipidemia

Approved Indication

Therapeutic area and approved indications in Germany: Hypercholesterolemia (HC), combined HC and hypertriglyceridemia with dominant HC, secondary prevention of cardiac events in patients with percutaneous coronary intervention (PCI).

Study Number

CXUO320BDE35

Title

A 16-week randomized, active-controlled, open-label, multicenter, 2-period cross-over study to investigate the effect of the combination of fluvastatin ER 80 mg and fenofibrate 200mg on HDL-C in comparison to the combination of simvastatin 20 mg and ezetimibe 10 mg in patients with metabolic syndrome

Phase of Development

IV

Study Start/End Dates

31-Jul-2006 to 21-Mar-2007

Study Design/Methodology

Randomized, active-controlled, open-label, multicenter cross-over study using a combination of Lescol (fluvastatin) extended release (ER) 80 mg and fenofibrate 200 mg, and a combination of simvastatin 20 mg and ezetimibe 10 mg in patients with metabolic syndrome.
The study duration includes a dietary-run in screening phase of 2 to 6 weeks and a treatment phase of 14 weeks with 2 weeks interruption between the 6-week active treatment periods.

Centres

8 centers in Germany

Publication

planned

Objectives

Primary objective(s)

To assess the efficacy of the combination of fluvastatin 80 mg and fenofibrate 200 mg in increasing HDL-C compared with the combination of simvastatin 20 mg and ezetimibe 10 mg after a treatment period of 6 weeks each in patients with type 2 diabetes/metabolic syndrome.

Secondary objective(s)

To compare the effects of combination therapy of fluvastatin 80 mg ER and fenofibrate 200 mg to the combination of simvastatin 20 mg and ezetimibe 10 mg on the number of patients reaching target levels of non-HDL-C < 130 mg/dl.

To compare the effects of the combination therapy of fluvastatin 80 mg ER and fenofibrate 200 mg to the combination of simvastatin 20 mg and ezetimibe 10 mg on LDL-C/HDL-C, Triglycerides, LDL 5+6 subfractions, and endothelial function (FDD) in a subgroup of patients.

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

Fluvastatin 80 mg (ER) tablets and Fenofibrate 200 mg capsules taken orally (=Fluva/Feno).

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

Fixed combination tablets with simvastatin 20 mg and ezetimibe 10 mg taken orally (=Simva/Ezetim)

Criteria for Evaluation

Primary variables

HDL-Cholesterol measured at the end of each treatment period.

Secondary variables

At the end of each treatment period:

-Number of patients reaching target levels of non-HDL-C <130mg/dl

- LDL-C/HDL-C

-Triglycerides

-LDL subfractions in a subgroup of patients

-Endothelial function (flow mediated dilation) in a subgroup of patients

Safety and tolerability

Adverse events (AEs), serious adverse events (SAEs), laboratory monitoring, vital signs, physical examination.

Pharmacology

none

Other

none

Statistical Methods

Intent to treat (ITT)

All randomized patients with at least one post-baseline efficacy measurement will be included in the intent-to-treat (ITT) data set for a given parameter. The ITT population will consist of all patients from the safety-population who have at least one post-baseline assessment of the primary endpoint in both study periods.

Per protocol

All ITT patients who: (a) meet the inclusion/exclusion criteria and (b) do not violate the protocol in a manner liable to affect the efficacy assessment will be included in the per-protocol popula-

tion.

The primary analysis was performed comparing treatments with respect to the primary efficacy parameter in an analysis of variance (ANOVA) model with factors treatment, period and patient. Adjusted (=LS-) as well as unadjusted means are presented for the treatment contrast together with its confidence interval and p-value. The confirmatory testing was performed on the two-sided 5% level; confidence intervals will be calculated as two-sided 95%.

Missing values have not been replaced. Patients without post-baseline efficacy data are not included in the ITT or the PP-population. Patients with measured values but with (serious) protocol violations were included with their obtained values for the ITT-analysis.

Secondary endpoints were analyzed analogous to the primary parameter.

Safety endpoints were analyzed descriptively.

No interim analysis was performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Written informed consent to participate in the study prior to any study procedures.
- Male or female subjects, age between 18-75 years inclusive.
- All women of child bearing potential must have a negative pregnancy test
- Metabolic Syndrome according to the IDF definition:
  Low plasma HDL-C (Men < 40 mg/dl ; Women < 50 mg/dl).
  Elevated waist circumference (men = 94 cm, women = 80cm)
  And one ore more of the following criteria:
  Triglycerides = 150 mg/dl
  Raised blood pressure (DBP = 85 mmHg and/or SBP = 130mmHg) or treated hypertension.
  Fasting plasma glucose= 100mg/dl.
  Previously diagnosed type 2 diabetes.

Main Exclusion criteria

- Dyslipidemia secondary to other causes such as nephrotic syndrome, autoimmune disease .
- Type 1 diabetes .
- HbA1c > 9.5%
- Unexplained serum creatine phosphokinase >2 x upper limit of normal
- History of myocardial infarction and/or cerebral stroke and/or unstable angina pectoris
- Known or suspected contraindications and warnings according to the country specific label for the investigational drugs

Number of Subjects

	Fluva/Feno	Simva/Ezetim
Planned N	59	59
Randomised n	73	72
Intent-to-treat population (ITT) n (%)	67 (91.8)	68 (94.4)
Completed n (%)	69 (94.5)	69 (95.8)
Withdrawn n (%)	4 (5.5)	3 (4.2)
Withdrawn due to adverse events n (%)	1 (1.4)	2 (2.8)
Withdrawn for other reasons n (%)	3 (4.1)	1 (1.4)

Demographic and Background Characteristics

Variable		Statistic	Total (N=75)
Age [yrs]		N	75
		Mean	56.0
		Std	10.3
		Min	23
		Median	56.0
		Max	79
	< 35 years	n (%)	1 (1.3)
	35-44 years	n (%)	9 (12.0)
	45-54 years	n (%)	24 (32.0)
	55-64 years	n (%)	22 (29.3)
	>= 65 years	n (%)	19 (25.3)
Sex	Male	n (%)	48 (64.0)
	Female	n (%)	27 (36.0)
Race	Caucasian	n (%)	74 (98.7)
	Other	n (%)	1 (1.3)
HDL-C [mg/dl]		Mean	34.8

Note that this was a cross-over study

Primary Objective Result(s)

Comparison of HDL-Cholesterol measured at the end of each study period. (ITT-population)

Parameter	Treatment	n	mean (SD)	LS-mean	95% CI (Treatment difference)	p
HDL-C (mg/dl)	Fluva/Feno	67	40.0 (9.36)	40.1	[-1.7 , 2.2]	0.7778
	Simva/Ezetim	68	39.8 (7.99)	39.8		

ANOVA model wth factors center, patient within center, period and treatment.

Secondary Objective Result(s)

Comparison of secondary endpoint parameters measured at the end of each study period. (ITT-population)

	Treatment	n	mean (SD)	LS-mean	95% CI (Treatment difference) (treatment	p
LDL-C/HDL-C	Fluva/Feno	67	2.6 (0.74)	2.6	[0.4 , 0.7]	<.0001
	Simva/Ezetim	68	2.0 (0.63)	2.0		
Triglycerides (mg/dl)	Fluva/Feno	67	144.8 (70.37)	143.7	[-46.7 , -14.0]	0.0004
	Simva/Ezetim	68	174.1 (80.75)	174.1		
LDL 5+6 (%)	Fluva/Feno	64	34.8 (9.21)	34.9	[-10.4 , -5.6]	<.0001
	Simva/Ezetim	68	42.9 (11.10)	42.9		
Endothelial function (FDD)	Fluva/Feno	19	7.2 (2.12)	7.2	[-0.6 , 0.8]	0.6844
	Simva/Ezetim	19	7.1 (2.15)	7.1		

ANOVA model with factors center, patient within center, period and treatment;

Fluva/Feno (N=68)	Simva/Ezetim (N=68)	Percent of Patients reaching target levels of non-HDL-C < 130 mg/dl					
		Difference			Odds Ratio		
n (%)	n (%)	%	95 % CI	p|Diff=0	OR	95 % CI	p|OR=1
67 (98.5)	68 (100)	-1.5	[-4.3 , 1.4]	0.3137	.		.

Safety Results

Adverse Events by System Organ Class and by Preferred Term

System organ class Preferred term	Total (N=75) n	 % of Patients	Fluva/Feno (N=73) n	 % of Patients	Simva/Ezetim (N=72) N	 % of Patients
All System Organ Classes						
No. of Patients with AEs	24	(32.0)	11	(15.1)	16	(22.2)
EYE DISORDERS						
CONJUNCTIVITIS	1	(1.3)	0	(0.0)	1	(1.4)
GASTROINTESTINAL DISORDERS						
ABDOMINAL PAIN	1	(1.3)	1	(1.4)	0	(0.0)
ABDOMINAL PAIN UPPER	1	(1.3)	1	(1.4)	0	(0.0)
DIARRHOEA	1	(1.3)	1	(1.4)	0	(0.0)
FLATULENCE	1	(1.3)	1	(1.4)	0	(0.0)
HAEMORRHOIDS	1	(1.3)	0	(0.0)	1	(1.4)
VOMITING	1	(1.3)	1	(1.4)	0	(0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
CHEST PAIN	2	(2.7)	1	(1.4)	1	(1.4)
FATIGUE	1	(1.3)	0	(0.0)	1	(1.4)
HEPATOBILIARY DISORDERS						
HEPATIC STEATOSIS	1	(1.3)	0	(0.0)	1	(1.4)
INFECTIONS AND INFESTATIONS						
ACUTE SINUSITIS	2	(2.7)	0	(0.0)	2	(2.8)
BRONCHITIS	2	(2.7)	1	(1.4)	1	(1.4)
GASTROENTERITIS	1	(1.3)	1	(1.4)	0	(0.0)
INFLUENZA	3	(4.0)	2	(2.7)	1	(1.4)
LARYNGITIS	1	(1.3)	0	(0.0)	1	(1.4)
NASOPHARYNGITIS	5	(6.7)	2	(2.7)	4	(5.6)
PHARYNGITIS	1	(1.3)	0	(0.0)	1	(1.4)
URINARY TRACT INFECTION	1	(1.3)	0	(0.0)	1	(1.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS						
PROCEDURAL NAUSEA	1	(1.3)	0	(0.0)	1	(1.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
MUSCLE SPASMS	1	(1.3)	0	(0.0)	1	(1.4)
MYALGIA	4	(5.3)	1	(1.4)	3	(4.2)
MYOPATHY	1	(1.3)	1	(1.4)	0	(0.0)

Cont.

System organ class	Total (N=75)		Fluva/Feno (N=73)		Simva/Ezetim (N=72)	
Preferred term	n	% of Patients	n	% of Patients	N	% of Patients
MYOSITIS	1	(1.3)	1	(1.4)	0	(0.0)
PAIN IN JAW	1	(1.3)	1	(1.4)	0	(0.0)
NERVOUS SYSTEM DISORDERS						
CARPAL TUNNEL SYNDROME	1	(1.3)	1	(1.4)	0	(0.0)
HEADACHE	2	(2.7)	0	(0.0)	2	(2.8)
SCIATICA	1	(1.3)	0	(0.0)	1	(1.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
COUGH	1	(1.3)	1	(1.4)	0	(0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
PRURITUS	1	(1.3)	1	(1.4)	0	(0.0)

Source : Post-text table 10.1-1. Treatment refers to the last treatment received before AE start.

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

System organ class	Fluva/Feno (N=73)		Simva/Ezetim (N=72)	
Preferred term	n	% of Patients	n	% of Patients
NASOPHARYNGITIS	2	(2.7)	4	(5.6)
MYALGIA	1	(1.4)	3	(4.2)
INFLUENZA	2	(2.7)	1	(1.4)
CHEST PAIN	1	(1.4)	1	(1.4)
ACUTE SINUSITIS	0	(0.0)	2	(2.8)
BRONCHITIS	1	(1.4)	1	(1.4)
HEADACHE	0	(0.0)	2	(2.8)

All other AEs reported only once

Serious Adverse Events and Deaths

	Novartis product	**Comparator**
No. (%) of subjects studied	73	72
No. (%) of subjects with AE(s)	11 (15.1)	16 (22.2)
Number (%) of subjects with serious or other significant events	n (%)	n (%)
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 14 March 2008
Date Inclusion on Novartis Clinical Trial Results Database 28 March 2008
Date of Latest Update 28 March 2008