EUDRA-CT

EudraCT: 2006-005906-30

Title of study

The Effect of Ezetimibe 10 mg, Simvastatin 20 mg and the combination of Simvastatin 20 mg plus 10 mg Ezetimibe on LDL-subfractions in patients with Type 2 Diabetes Mellitus

Sponsor

Medical Center - University of Freiburg
Hugstetter Straße 55
79106 Freiburg
Germany

Name of finished product / Name of active substance

Ezetrol 10 mg / ezetimibe

Zocor 20 mg / simvastatin

Inegy 10/20 mg / ezetimibe + simvastatin

Investigators and trial centers

Principal Investigator

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Ezetimibe alone and in combination lowers the concentration of small, dense low-density lipoproteins in type 2 diabetes mellitus
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Trial period

First enrolment: 06.11.2007

Last completed: 19.05.2010

Phase of development

Investigator-initiated trial, Phase IV

Objectives

Primary Objectives
Effect of 6 weeks treatment with ezetimibe 10 mg (E), simvastatin 20 mg (S) and combination therapy of both drugs (SE) on concentrations of small dense LDL (sdLDL).

Secondary objectives
Effect of 6 weeks treatment with ezetimibe 10 mg (E), simvastatin 20 mg (S) and combination therapy of both drugs (SE) on concentrations of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides.

Methodology

- Phase-IV study
- Multicentre
- Randomized
- Open-labeled
  - → Active Comparator (E):
    Ezetimibe 10mg/d oral intake of ezetimibe 10mg per day for six weeks after wash-out (Drug: Ezetimibe 10 mg, other Name: Ezetrol 10 mg)
  - → Active Comparator (S):
    Simvastatin 20 mg per day oral intake of simvastatin 20 mg per day for six weeks after wash-out (Drug: Simvastatin 20 mg, other Name: Zocor MSD)
  - → Active Comparator (SE):
    Ezetimibe 10 mg/d and Simvastatin 20mg/d oral intake of ezetimibe 10 mg and simvastatin 20 mg per day for six weeks after wash-out (Drug: Ezetimibe 10 mg/Simvastatin 20 mg, other Name: Inegy 10/20)

Number of patients

- Target number:
  60 patients with well controlled Type 2 Diabetes (HbA1c ≤ 8,0 %) und LDL-Cholesterin ≤ 160 mg/dl) matching the above mentioned inclusion and exclusion criteria.
- Number of screened patients:
  56 patients were screened for sdLDL.
- Randomized patients:
  41 were randomized to one of the three treatment arms.

- Number of Patients with complete subfraction profiles and therefore eligible for final anlysis:
  Complete LDL-subfraction profiles were available from 40 patients (12 E; 14 S and 14 SE) recruited from 2 study centres.

Diagnosis and main inclusion/exclusion criteria

Inclusion criteria:

- men > 18 and ≤ 75 years
- post-menopausal women ≤ 75 years (follicle stimulating hormone (FSH) >30 mIU/ml, women > 60 years FSH > 20 mIU/ml)
- well controlled diabetes mellitus type II (glycohaemoglobin ≤ 8,0 %)
- LDL-cholesterol ≤ 160 mg/dl
- LDL-subfractions: concentration of apoB-100 in dLDL (LDL-5 und LDL-6) > 20 mg/dl
- written informed consent

Exclusion criteria:

- participation in a clinical trial within the last 30 d before screening- visit
- patient is unable to give written informed consent
- Body mass index <15 kg/m² and > 35 kg/m²
- clinical atherosclerotic disease (coronary heart disease, peripheral artery disease, carotid artery disease)
- malignoma
- uncontrolled arterial hypertension (>160/>100 mmHg)
- clinically relevant disease of liver and/or kidneys
- clinically relevant endocrinally or hematologic problems
- allergy to study medication (Ezetimibe and/or Simvastatin)
- alcohol- or drug abuse
- laboratory: alanine aminotransferase, aspartate aminotransferase, total bilirubin > 3 x ULN, creatine kinase > 5 x ULN
- Concurrent treatment with potent CYP3A4-inhibitors (e.g. itraconazole, ketoconazole, HIV-protease-inhibitors, erythromycin, clarithromycin, telithromycin und nefazodone)
- other relevant diseases

Test product, dose and mode of administration, batch number

Ezetrol 10 mg, daily oral administration, batch numbers 276232, 263595

Zocor 20 mg, daily oral administration, batch numbers 280112, 263463

Inegy 10/20 mg, daily oral administration, batch numbers S6582, R6117

Duration of treatment

6 weeks of treatment with either Ezetrol 10 mg, Zocor 20 mg or Inegy 10/20 mg.

Criteria for evaluation

- Primary outcome measures:
  Change of the concentration of apolipoprotein B (ApoB) in dense Low Densitiy Lipoprotein (dLDL) from baseline with ezetimibe, simvastatin or the combination of both drugs [Time Frame: baseline and 6 weeks]
- Secondary Outcome Measures:
  Change of the concentrations of total cholesterol, Low Densitiy Lipoprotein (LDL) –Cholesterol, High Density Lipoprotein (HDL) –Cholesterol, triglycerides [Time Frame: baseline and 6 weeks]

Statistical analysis

- Clinical and biochemical baseline characteristics are expressed as means ± standard deviations or medians and 25th and 75th percentile as appropriate
- Changes in parameters between baseline and after 6 weeks of treatment with either ezetimibe 10 mg, simvastatin 20 mg, or combination of both were compared using the non-parametric Wilcoxon signed ranks test.
- Comparison of drug effects between treatment groups was carried out with an univariate ANOVA procedure.
- Changes were considered statistically significant if p-value was < 0.05.

Results

***Baseline characteristics*:**

	All patients	Ezitimibe 10 mg	Simvastatin 20 mg	Combination Therapy	
n	40	12	14	14	p-value
Age, y	63.7±6.9	65.2±5.4	62.6±6.6	63.6±8.4	0.611
Gender female, % (n)	40 (16)	42 (5)	50 (7)	29 (4)	0.500
Body mass index, kg/m²	31.3±5.2	31.5±4.4	31.2±6.2	31.1±5.1	0.942
Hypertension, % (n)	83 (33)	92 (11)	86 (12)	71 (10)	0.142
HbA1c, %	6.8±0.9	6.6±0.8	6.9±1.1	6.9±0.8	0.708
Cholesterol, mg/dL	226±39	234±57	219±27	225±32	0.394
Triglycerides, mg/dL (25^{th} – 75^{th} percentile)	182 (149-263)	160 (149 – 321)	185 (119 - 264)	188 (151-274)	0.540
LDL cholesterol, mg/dL	113±31	123±36	106±19	110±37	0.257
HDL cholesterol mg/dL	41.0±10.1	40.2±12.4	46.0±10.0	36.8±7.2	0.140
Lp(a), mg/dL (25^{th} – 75^{th} percentile)	10.5 (4.0 – 21.8)	11.5 (5.0 -51.0)	6.5 (3.5 – 26.0)	10.5 (5.5 – 28.5)	0.977

ApoB in sdLDL (LDL-5 & LDL-6), mg/L	304±121	347±142	279±115	294±104	0.479

Effect of six weeks treatment on lipid parameters

Ezitimibe 10 mg

	baseline	treatment	p-value
sdLDL cholesterol, mg/dL	42.6±18.2	32.7±12.0	0.029
Cholesterol, mg/dL	234±57	202±47	0.004
Triglycerides, mg/dL (25^{th} – 75^{th} percentile)	160 (149 - 321)	168 (133 - 238)	0.307
LDL cholesterol, mg/dL	123±36	105±33	0.006
HDL cholesterol mg/dL	40.2±12.4	41.7±12.3	0.356
Lp(a), mg/dL (25^{th} – 75^{th} percentile)	11.5 (5.0 -51.0)	7.5 (4.0-61.3)	0.476
HbA1c, %	6.6±0.8	6.6±0.7	0.295

Simvastatin 20 mg

	baseline	treatment	p-value
sdLDL cholesterol, mg/dL	34.6±14.3	25.0±9.3	0.007
Cholesterol, mg/dL	219±27	171±28	<0.001
Triglycerides, mg/dL (25^{th} – 75^{th} percentile)	185 (119 - 264)	180 (94 - 223)	0.331
LDL cholesterol, mg/dL	106±19	72±17	<0.001
HDL cholesterol mg/dL	46.0±10.0	49.3±12.0	0.087
Lp(a), mg/dL (25^{th} – 75^{th} percentile)	6.5 (3.5 – 26.0)	8.0 (3.0-35.5)	0.047
HbA1c, %	6.9±1.1	6.9±1.1	1.000

Combination

	Baseline	treatment	p-value
sdLDL cholesterol, mg/dL	36.9±11.4	23.1±5.6	0.002
Cholesterol, mg/dL	225±32	153±26	<0.001
Triglycerides, mg/dL (25^{th} – 75^{th} percentile)	188 (151-274)	132 (114 - 235)	0.116
LDL cholesterol, mg/dL	110±37	62±17	<0.001
HDL cholesterol mg/dL	36.8±7.2	42.1±10.9	0.014
Lp(a), mg/dL (25^{th} – 75^{th} percentile)	10.5 (5.5 – 28.5)	8.0 (2.0-23.0)	0.964
HbA1c, %	6.9±0.8	6.8±0.8	0.250

Safety results:

Adverse events:

Ezetimibe:	
Possible relation to study medication	flatulence pain thumb basal joint left hand and right shoulder muscle soreness after starting fitness studio
Not related to study medication	increase of serum creatinine after intake of diclofenac toothache eczema psoriasis torticollis influenzal infection
Simvastatine:	
Possible relation to study medication	constipation
Not related to study medication	common cold flu-like infection shoulder-arm-syndrome

Ezetimibe/Simavastatine combination:	
Possible relation to study medication	none
Not related to study medication	gastroenteritis cough small necrosis on right thumb after blister pain right shoulder

No adverse events with a certain relation to the study medication were observed.

Serious adverse events:

One serious adverse event (fracture of left hip joint) with an unlikely relation to the study medication (ezetimibe/simvastatine combination) was reported.

Summary – Conclusions: Efficacy Results, Safety Results, Conclusion

In patients presenting with a preponderance of sdLDL in diabetes mellitus type 2 ezetimibe, alone or in combination with simvastatin, clearly reduces concentrations of sdLDL, the primary efficacy parameter. The combination of ezetimibe/simvastatine reduced sdLDL the most (-37.4%), followed by simvastatine (-27.7%) and ezetimibe alone (-23.2%).

Secondary parameters cholesterol (ezetimibe -13.7%, simvastatine -21.9% and ezetimibe/simvastatine combination -32.0%) and LDL-cholesterol ((ezetimibe -14.6%, simvastatine -31.1% and ezetimibe/simvastatine combination -43.6%) were also reduced significantly. Triglycerides were not changed over the treatment period, irrespective of the treatment group. HDL-cholesterol increased in the simvastine group (+7.2%) and the ezetimibe/simvastatine group (+14.4%).

All three treatment options were well tolerated. No adverse events with a certain causal relation to the medicinal products were observed.