Ezetimibe and Simvastatin in Primary Hypercholesterolemia, Diabetes Mellitus Type 2, and Coronary Heart Disease (COMPLETED)

This study has been completed.

Sponsor:
Merck Sharp & Dohme Corp.

Collaborator:
Schering-Plough

Information provided by (Responsible Party):
Merck Sharp & Dohme Corp.

ClinicalTrials.gov Identifier:
NCT00423488

First received: January 17, 2007
Last updated: September 18, 2015
Last verified: September 2015
History of Changes

Purpose

This multicenter, randomized, double-blind, placebo-controlled study will assess, after 6 weeks of dosing, whether co-administration of ezetimibe 10 mg with simvastatin 20 mg will be more effective than treatment with doubling the dose of simvastatin to 40 mg alone in reducing low-density lipoprotein-cholesterol (LDL-C) concentrations and in achieving the National Cholesterol Expert Panel (NCEP) III LDL-C target goal of <2.6 mmol/L (<100 mg/dL) for subjects with diabetes mellitus and coronary heart disease.

Condition	Intervention	Phase
Hypercholesterolemia Diabetes Mellitus, Type 2 Coronary Disease	Drug: Ezetimibe 10 mg Drug: Simvastatin 20 mg Drug: Ezetimibe Placebo Drug: Simvastatin Placebo	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Official Title: A Multicenter, Randomized, Parallel-Groups, Double-Blind Placebo Controlled Study Comparing the Efficacy, Safety, and Tolerability of Co-administration of Ezetimibe 10 mg With Ongoing Treatment With Simvastatin 20 mg Versus Doubling the Dose of Simvastatin in Subjects With Primary Hypercholesterolemia Diabetes Mellitus Type 2 and Coronary Heart Disease

Resource links provided by NLM:

MedlinePlus related topics: Cholesterol Coronary Artery Disease Diabetes Type 2 Diabetic Heart Disease Heart Diseases

Drug Information available for: Simvastatin Ezetimibe

U.S. FDA Resources

Further study details as provided by Merck Sharp & Dohme Corp.:

Primary Outcome Measures:

- Percent Change in Low-Density Lipoprotein Cholesterol (LDL-C) From Baseline to Endpoint, After 6 Weeks of Treatment [Time Frame: 6 weeks of treatment (from Baseline to Endpoint)] [Designated as safety issue: No]

Enrollment:	93
Study Start Date:	July 2005
Study Completion Date:	February 2007
Primary Completion Date:	February 2007 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Ezetimibe 10 mg + Simvastatin Placebo + Simvastatin 20 mg Participants were instructed to take one 10-mg ezetimibe tablet and one simvastatin placebo tablet orally in the evening every day for six weeks in addition to their daily, oral, open-label, 20-mg simvastatin tablet.	Drug: Ezetimibe 10 mg 1 x 10-mg tablet, provided as blinded study treatment Drug: Simvastatin 20 mg 1 x 20-mg tablet, provided as open-label study treatment Drug: Simvastatin Placebo 1 tablet matching 20-mg simvastatin tablet, provided as blinded study treatment
Active Comparator: Ezetimibe Placebo + Simvastatin 40 mg Participants were instructed to take one ezetimibe placebo tablet and one simvastatin 20-mg tablet orally in the evening every day for six weeks in addition to their daily, oral, open-label, 20-mg simvastatin tablet.	Drug: Simvastatin 20 mg 1 x 20-mg tablet, provided as open-label study treatment Drug: Ezetimibe Placebo 1 tablet matching ezetimibe 10-mg tablet, provided as blinded study treatment Drug: Simvastatin 20 mg 1 x 20-mg tablet, provided as blinded study treatment

Eligibility

Ages Eligible for Study:	18 Years to 75 Years
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Subject must have diabetes mellitus type 2 (fasting plasma glucose >7 mmol/L [126 mg/dL]) of at least 12 months duration at Visit 3 and must be adequately controlled (glycated hemoglobin [HbA1c] <=9.0%). Subjects must not have had a change in antidiabetic pharmacotherapy [i.e. changes in dosage (with the exception of +/- 10 units of insulin) or addition of new medication] or experience recent history of repeated hypoglycemia or unstable glycemic control within 3 months of Visit (Baseline Visit).
- Subjects must have documented coronary heart disease (CHD). For the purposes of this study, CHD will include one or more of the following features: documented stable angina with evidence of ischemia on exercise testing); history of myocardial infarction; history of percutaneous transluminal coronary intervention (PCTI) with or without stent placement); symptomatic peripheral vascular disease (claudication); documented history of atherothrombotic cerebrovascular disease; and/or documented history of unstable angina or non-Q wave myocardial infarction.
- Subjects must have a low-density lipoprotein cholesterol (LDL-C) concentration >=2.6 mmol/L (100 mg/dL) to <=4.1 mmol/L (160 mg/dL) using the Friedewald calculation available at the time of randomization Visit 3 (Baseline Visit).

- Subjects must have triglyceride concentrations of <3.99 mmol/L (350 mg/dL) at Visit 3 (Baseline Visit).
- Subject must be currently taking simvastatin 20 mg daily and by history has taken 80% of daily evening doses for the 6 weeks prior to Visit 3 (Baseline Visit).
- Subject must be >=18 years and <=75 years of age.
- Subjects must have maintained a cholesterol lowering diet and exercise program for at least 4 weeks prior to Screening (Visit 2) and be willing to continue the same diet and exercise program during the study.
- Subjects must have liver transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) <50% above the upper limit of normal, with no active liver disease, and creatinine kinase (CK)<50% above the upper limit of normal at Visit 3 (Baseline Visit).
- Clinical laboratory tests (complete blood count (CBC), blood chemistries, urinalysis) must be within normal limits or clinically acceptable to the investigator at Visit 3 (Baseline Visit).
- Subjects must report a stable weight history for at least 4 weeks prior to entry into study at Visit 3 (Baseline Visit).
- Women receiving hormonal therapy, including hormone replacement, any estrogen antagonist/agonist, or oral contraceptives, must have been maintained on a stable dose and regimen for at least 8 weeks and be willing to continue the same regimen for the duration of the study.
- Women of childbearing potential (includes women who are less than 1 year postmenopausal and women who become sexually active) must be using an acceptable method of birth control (e.g., hormonal contraceptive, medically-prescribed intrauterine device (IUD), condom in combination with spermicide) or be surgically sterilized (e.g., hysterectomy or tubal ligation).
- Subjects must be free of any clinically significant diseases other than diabetes mellitus or coronary heart disease that would interfere with study evaluations.
- Subjects must understand and be able to adhere to the dosing and visit schedules, and must agree to remain on their cholesterol-lowering diet and their exercise regimen for the duration of the study
- Subjects must demonstrate their willingness to participate in the study and comply with its procedures by signing a written informed consent.

Exclusion Criteria:

- Subjects whose body mass index (BMI = weight[kg]/height[m]**2) is >=35 kg/m**2 at Visit 3 (Baseline Visit).
- Subjects who consume >14 alcoholic drinks per week. (A drink is: a can of beer, glass of wine, or single measure of spirits).
- Any condition or situation which, in the opinion of the investigator, might pose a risk to the subject or interfere with participation in the study.
- Women who are pregnant or nursing.
- Congestive heart failure defined by New York Heart Association (NYHA) as Class III or IV.
- Uncontrolled cardiac arrhythmia.
- Myocardial infarction, acute coronary insufficiency, coronary artery bypass surgery, or angioplasty within 3 months of Visit 3 (Baseline Visit).
- Unstable or severe peripheral artery disease within 3 months of Visit 3 (Baseline Visit).
- Newly diagnosed or currently unstable angina pectoris.
- Uncontrolled hypertension (treated or untreated) with systolic blood pressure >160 mmHg or diastolic >100 mmHg at Visit 3 (Baseline Visit).
- Uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins, i.e., secondary causes of hyperlipidemia, such as secondary hypercholesterolemia due to hypothyroidism (thyroid stimulating hormone [TSH] above upper limit of normal) at Visit 3. Subjects with a history of hypothyroidism who are on a stable therapy of thyroid hormone replacement for at least 6 weeks are eligible for enrollment if TSH levels are within normal limits at Visit 3 (Baseline Visit).
- Impaired renal function (creatinine >2.0 mg/dL) or nephrotic syndrome at Visit 3 (Baseline Visit).
- Disorders of the hematologic, digestive, or central nervous systems including cerebrovascular disease and degenerative disease that would limit study evaluation or participation.
- Known human immunodeficiency virus (HIV) positive.
- Cancer within the past 5 years (except for successfully treated basal and squamous cell carcinomas).
- History of mental instability, drug/alcohol abuse within the past 5 years, or major psychiatric illness not adequately controlled and stable on pharmacotherapy.
- Subjects who have not observed the designated wash-out period for any of the prohibited medications.
- Subjects currently consuming large amounts of grapefruit juice (>1 liter/day).
- Oral corticosteroids, unless used as replacement therapy for pituitary/adrenal disease and the subject is on a stable regimen for at lest 6 weeks prior to Visit 3 (Baseline Visit).
- Subjects who are currently using cardiovascular medication (e.g., antihypertensive, antiarrhythmic) and have not been on a stable regimen for at least 6 weeks prior to Visit 3 (Baseline Visit) and it is expected to change during the study.
- Subjects who are currently using psyllium, other fiber-based laxatives, and/or any other over-the-counter (OTC) therapy known to affect serum lipid levels (phytosterol margarine), and have not been on a stable regimen for at least 5 weeks prior to study entry Visit 3 (Baseline Visit) and who do not agree to remain on this regimen throughout the study.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

No Contacts or Locations Provided

More Information

Publications:

Bardini G, Giorda CB, Pontiroli AE, Le Grazie C, Rotella CM. Ezetimibe + simvastatin versus doubling the dose of simvastatin in high cardiovascular risk diabetics: a multicenter, randomized trial (the LEAD study). Cardiovasc Diabetol. 2010 May 21;9:20. doi: 10.1186/1475-2840-9-20.

Additional publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Rotella CM, Zaninelli A, Le Grazie C, Hanson ME, Gensini GF. Ezetimibe/simvastatin vs simvastatin in coronary heart disease patients with or without diabetes. Lipids Health Dis. 2010 Jul 27;9:80. doi: 10.1186/1476-511X-9-80.

Responsible Party:	Merck Sharp & Dohme Corp.
ClinicalTrials.gov Identifier:	NCT00423488 History of Changes
Other Study ID Numbers:	**P04037**
Study First Received:	January 17, 2007
Results First Received:	February 17, 2010
Last Updated:	September 18, 2015
Health Authority:	Italy: AIFA Agenzia Italiana del Farmaco- Rome

Additional relevant MeSH terms:

Coronary Artery Disease	Lipid Metabolism Disorders
Coronary Disease	Metabolic Diseases
Diabetes Mellitus	Vascular Diseases
Diabetes Mellitus, Type 2	Ezetimibe
Heart Diseases	Simvastatin
Hypercholesterolemia	Anticholesteremic Agents
Myocardial Ischemia	Antimetabolites
Arterial Occlusive Diseases	Enzyme Inhibitors
Arteriosclerosis	Hydroxymethylglutaryl-CoA Reductase Inhibitors
Cardiovascular Diseases	Hypolipidemic Agents
Dyslipidemias	Lipid Regulating Agents
Endocrine System Diseases	Molecular Mechanisms of Pharmacological Action
Glucose Metabolism Disorders	Pharmacologic Actions
Hyperlipidemias	Therapeutic Uses

ClinicalTrials.gov processed this record on March 30, 2016

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Results First Received: February 17, 2010

Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Investigator, Outcomes Assessor); Primary Purpose: Treatment
Conditions:	Hypercholesterolemia Diabetes Mellitus, Type 2 Coronary Disease
Interventions:	Drug: Ezetimibe 10 mg Drug: Simvastatin 20 mg Drug: Ezetimibe Placebo Drug: Simvastatin Placebo

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
No text entered.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
No text entered.

Reporting Groups

	Description
Ezetimibe 10 mg + Simvastatin Placebo + Simvastatin 20 mg	Participants were instructed to take one 10-mg ezetimibe tablet and one simvastatin placebo tablet orally in the evening every day for six weeks in addition to their daily, oral, 20-mg simvastatin tablet.
Ezetimibe Placebo + Simvastatin 40 mg	Participants were instructed to take one ezetimibe placebo tablet and one simvastatin 20-mg tablet orally in the evening every day for six weeks in addition to their daily, oral, 20-mg simvastatin tablet.

Participant Flow: Overall Study

	Ezetimibe 10 mg + Simvastatin Placebo + Simvastatin 20 mg	Ezetimibe Placebo + Simvastatin 40 mg
STARTED	**42**	**51**
COMPLETED	**37**	**50**
NOT COMPLETED	**5**	**1**
No evidence of study drug intake	**2**	**1**
No post baseline data	**3**	**0**

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
Ezetimibe 10 mg + Simvastatin Placebo + Simvastatin 20 mg	Participants were instructed to take one 10-mg ezetimibe tablet and one simvastatin placebo tablet orally in the evening every day for six weeks in addition to their daily, oral, 20-mg simvastatin tablet.
Ezetimibe Placebo + Simvastatin 40 mg	Participants were instructed to take one ezetimibe placebo tablet and one simvastatin 20-mg tablet orally in the evening every day for six weeks in addition to their daily, oral, 20-mg simvastatin tablet.
Total	Total of all reporting groups

Baseline Measures

	Ezetimibe 10 mg + Simvastatin Placebo + Simvastatin 20 mg	Ezetimibe Placebo + Simvastatin 40 mg	Total
Number of Participants [units: participants]	**42**	**51**	**93**

Age [units: years] Mean (Standard Deviation)	**65.0 (6.5)**	**63.9 (6.1)**	**64.4 (6.3)**
Gender [units: participants]			
Female	**18**	**12**	**30**
Male	**24**	**39**	**63**
Region of Enrollment [units: participants]			
Italy	**42**	**51**	**93**

Outcome Measures

1. Primary: Percent Change in Low-Density Lipoprotein Cholesterol (LDL-C) From Baseline to Endpoint, After 6 Weeks of Treatment [Time Frame: 6 weeks of treatment (from Baseline to Endpoint)]

Hide Outcome Measure 1

Measure Type	Primary
Measure Title	Percent Change in Low-Density Lipoprotein Cholesterol (LDL-C) From Baseline to Endpoint, After 6 Weeks of Treatment
Measure Description	No text entered.
Time Frame	6 weeks of treatment (from Baseline to Endpoint)
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat population only.

Reporting Groups

	Description
Ezetimibe 10 mg + Simvastatin Placebo + Simvastatin 20 mg	Participants were instructed to take one 10-mg ezetimibe tablet and one simvastatin placebo tablet orally in the evening every day for six weeks in addition to their daily, oral, 20-mg simvastatin tablet.
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Measured Values

	Ezetimibe 10 mg + Simvastatin Placebo + Simvastatin 20 mg	**Ezetimibe Placebo + Simvastatin 40 mg**
Number of Participants Analyzed [units: participants]	**37**	**50**
Percent Change in Low-Density Lipoprotein Cholesterol (LDL-C) From Baseline to Endpoint, After 6 Weeks of Treatment [units: percentage change]	**-32.2 (15.7)**	**-20.8 (20.1)**

Mean (Standard Deviation)		

Statistical Analysis 1 for Percent Change in Low-Density Lipoprotein Cholesterol (LDL-C) From Baseline to Endpoint, After 6 Weeks of Treatment

Groups [1]	All groups
Method [2]	ANOVA
P Value [3]	0.005
least-squares means [4]	-11.5
95% Confidence Interval	-19.4 to -3.5

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	The analysis of variance (ANOVA) model included term of treatment effect. If more than one basal value was available, the latest was used.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	No text entered.
Additional Description	The ezetimibe 10 mg + simvastatin placebo + simvastatin 20 mg safety population is comprised of 40 subjects as there was no evidence of study drug intake for 2 of the 42 randomized. The ezetimibe placebo + simvastatin 40 mg safety population is comprised of 50 participants as there was no evidence of study drug intake for 1 of the 51 randomized.

Reporting Groups

	Description
Ezetimibe 10 mg + Simvastatin Placebo + Simvastatin 20 mg	Participants were instructed to take one 10-mg ezetimibe tablet and one simvastatin placebo tablet orally in the evening every day for six weeks in addition to their daily, oral, 20-mg simvastatin tablet.
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Serious Adverse Events

	Ezetimibe 10 mg + Simvastatin Placebo + Simvastatin 20 mg	Ezetimibe Placebo + Simvastatin 40 mg
Total, serious adverse events		

# participants affected / at risk	**1/40 (2.50%)**	**0/50 (0.00%)**
Injury, poisoning and procedural complications		
Upper Limb Fracture † 1		
# participants affected / at risk	**1/40 (2.50%)**	**0/50 (0.00%)**
# events	**1**	**0**

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA (9.1)

Other Adverse Events

Hide Other Adverse Events

Time Frame	No text entered.
Additional Description	The ezetimibe 10 mg + simvastatin placebo + simvastatin 20 mg safety population is comprised of 40 subjects as there was no evidence of study drug intake for 2 of the 42 randomized. The ezetimibe placebo + simvastatin 40 mg safety population is comprised of 50 participants as there was no evidence of study drug intake for 1 of the 51 randomized.

Frequency Threshold

Threshold above which other adverse events are reported	5%

Reporting Groups

	Description
Ezetimibe 10 mg + Simvastatin Placebo + Simvastatin 20 mg	Participants were instructed to take one 10-mg ezetimibe tablet and one simvastatin placebo tablet orally in the evening every day for six weeks in addition to their daily, oral, 20-mg simvastatin tablet.
Ezetimibe Placebo + Simvastatin 40 mg	Participants were instructed to take one ezetimibe placebo tablet and one simvastatin 20-mg tablet orally in the evening every day for six weeks in addition to their daily, oral, 20-mg simvastatin tablet.

Other Adverse Events

	Ezetimibe 10 mg + Simvastatin Placebo + Simvastatin 20 mg	**Ezetimibe Placebo + Simvastatin 40 mg**
Total, other (not including serious) adverse events		
# participants affected / at risk	**0/40 (0.00%)**	**0/50 (0.00%)**

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data
No text entered.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.
There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.
The agreement is: ☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo. ☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo. Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed. ☑ **Restriction Description:** Investigator agrees not to publish or publicaly present results without prior written authorization from the sponsor, except than for the dispositions provided for in Ministerial Circular n.6 of 02 SEP 2002 and, particularly, disposition n.1a) The investigator further agrees to provide 30 days written notice to the sponsor prior to submission for publication or presentation to permit the sponsor to review copies of material(including text for oral presentation) that report study results.

Results Point of Contact:

Name/Title: Senior Vice President, Global Clinical Development
Organization: Merck Sharp & Dohme Corp.
e-mail: ClinicalTrialsDisclosure@merck.com

Publications of Results:

Bardini G, Giorda CB, Pontiroli AE, Le Grazie C, Rotella CM. Ezetimibe + simvastatin versus doubling the dose of simvastatin in high cardiovascular risk diabetics: a multicenter, randomized trial (the LEAD study). Cardiovasc Diabetol. 2010 May 21;9:20. doi: 10.1186/1475-2840-9-20.

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