Merck Carotid Atherosclerosis Trial (MK-0000-111)(COMPLETED) (MCAT)

This study has been completed.

Sponsor:
Merck Sharp & Dohme Corp.

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

ClinicalTrials.gov Identifier:
NCT00804843

First received: December 8, 2008
Last updated: September 28, 2015
Last verified: September 2015
History of Changes

Purpose

This study will examine the effect of statin and niacin therapy on carotid plaque biomarkers

Condition	Intervention	Phase
Carotid Atherosclerosis	Drug: Atorvastatin/niacin extended-release Drug: Atorvastatin Drug: Simvastatin	Phase 2

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

Official Title: A Randomized Clinical Trial to Evaluate the Effects of High Dose Statin and Niacin Therapy on Excised Plaque Biomarkers in Patients Undergoing Carotid Endarterectomy (CEA)

Resource links provided by NLM:

MedlinePlus related topics: Atherosclerosis Statins

Drug Information available for: Niacin Niacinamide Simvastatin Atorvastatin Atorvastatin calcium

U.S. FDA Resources

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

Primary Outcome Measures:

- Composite Score of Plaque Inflammation/Stability Gene Expression as Assayed by Ribonucleic Acid (RNA) Taqman Analysis [Time Frame: At

time of carotid endarterectomy (after 4 to 12 weeks of dosing)] [Designated as safety issue: No]

Excised carotid plaques were evaluated for the gene expression of 60 biomarkers associated with inflammation ("Hot" biomarkers) & 25 biomarkers associated with stability ("Cold" biomarkers). Each biomarker was assayed using a quantitative polymerase chain reaction method and results were reported as a Cycle Threshold, (Ct). A Composite Score was calculated by averaging the Ct for each of the 25 "cold" genes, and subtracting the average Ct for the 60 "hot" genes. A higher composite score was associated with greater inflammation and a lower score was associated with stability (non-inflamed).

- Plaque Instability Protein Composite Score [Time Frame: At time of carotid endarterectomy (after 4 to 12 weeks of dosing)] [Designated as safety issue: No]

  Each excised plaque was analyzed using an assay of 20 proteins that reflect plaque composition and inflammation. Each protein was assigned scaled signs, with a lower (negative) sign associated with plaque stability and a higher (positive) sign associated with plaque inflammation/instability. The Composite Score was the average amounts of all the 20 proteins with their associated signs. A higher Composite Score is associated with more plaque instability.

- Total Cholesterol and Free Cholesterol Measured by Enzymatic Chromogenic Assay [Time Frame: At time of carotid endarterectomy (after 4 to 12 weeks of dosing)] [Designated as safety issue: No]

  Cholesterol ester was to be calculated by the following formula: Cholesterol Ester = Total Cholesterol - Free Cholesterol.

Enrollment:	100
Study Start Date:	April 2009
Study Completion Date:	October 2010
Primary Completion Date:	October 2010 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Statin 80 mg + Niacin extended-release (ER) Participants in Russia and Brasil will receive 80 mg Simvastatin + niacin. All other participants will receive 80 mg Atorvastatin + niacin.	Drug: Atorvastatin/niacin extended-release 80 mg tablet atorvastatin once daily, 10 mg tablet placebo to atorvastatin once daily, and niacin extended-release tablet starting at 500 mg daily and titrating to 2g daily. Treatment will be from 4 to 12 weeks. Other Name: Lipitor, Niaspan Drug: Simvastatin (Russia and Brazil) 80 mg tablet simvastatin once daily, 10 mg tablet placebo to simvastatin once daily, and niacin extended-release tablet starting at 500 mg daily and titrating to 2g daily. Treatment will be from 4 to 12 weeks. Other Name: Zocor
Active Comparator: Statin 10 mg Participants in Russia and Brasil will receive 10 mg Simvastatin. All other participants will receive 10 mg Atorvastatin.	Drug: Atorvastatin 10 mg tablet atorvastatin once daily, 80 mg tablet placebo to atorvastatin once daily, and placebo to niacin extended-release tablet starting at 500 mg daily and titrating to 2g daily. Treatment will be from 4 to 12 weeks. Other Name: Lipitor Drug: Simvastatin (Russia and Brazil) 10 mg tablet simvastatin once daily, 80 mg tablet placebo to simvastatin once daily, and placebo to niacin extended-release tablet starting at 500 mg daily and titrating to 2g daily. Treatment will be from 4 to 12 weeks. Other Name: Zocor

Eligibility

Ages Eligible for Study:	18 Years to 90 Years
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Patient is diagnosed with carotid stenosis AND is scheduled to undergo carotid endarterectomy

- Female patients of reproductive potential must abstain from sex or use an acceptable method of birth control through out the study

Exclusion Criteria:

- Patient must undergo CEA less than 4 weeks after entering study
- Patient has recent history of acute coronary syndrome
- Patient has has coronary artery bypass graft surgery within 30 days of study start
- Patient has thyroid disease that has not been treated for more than 6 weeks
- Patient has donated blood within 8 weeks of study start
- Patient has poorly controlled diabetes mellitis
- Patient has human immunodeficiency virus (HIV) or Hepatitis B or C
- Patient is taking warfarin or other anticoagulants
- Patient is taking hormone replacement therapy

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.

Please refer to this study by its ClinicalTrials.gov identifier: NCT00804843

Sponsors and Collaborators

Merck Sharp & Dohme Corp.

Investigators

Study Director: Medical Monitor Merck Sharp & Dohme Corp.

More Information

Responsible Party:	Merck Sharp & Dohme Corp.
ClinicalTrials.gov Identifier:	NCT00804843 History of Changes
Other Study ID Numbers:	0000-111 2008_598
Study First Received:	December 8, 2008
Results First Received:	December 21, 2011
Last Updated:	September 28, 2015
Health Authority:	United States: Food and Drug Administration

Additional relevant MeSH terms:

Atherosclerosis	Anticholesteremic Agents
Carotid Artery Diseases	Antimetabolites
Arterial Occlusive Diseases	Cardiovascular Agents
Arteriosclerosis	Enzyme Inhibitors
Brain Diseases	Growth Substances
Cardiovascular Diseases	Hydroxymethylglutaryl-CoA Reductase Inhibitors
Central Nervous System Diseases	Hypolipidemic Agents
Cerebrovascular Disorders	Lipid Regulating Agents
Nervous System Diseases	Micronutrients
Vascular Diseases	Molecular Mechanisms of Pharmacological Action
Atorvastatin	Pharmacologic Actions
Niacin	Physiological Effects of Drugs
Niacinamide	Therapeutic Uses
Nicotinic Acids	Vasodilator Agents
Simvastatin	Vitamin B Complex

ClinicalTrials.gov processed this record on April 13, 2016

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History of Changes

Results First Received: December 21, 2011

Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Investigator); Primary Purpose: Treatment
Condition:	Carotid Atherosclerosis
Interventions:	Drug: Atorvastatin/niacin extended-release Drug: Atorvastatin Drug: Simvastatin

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
Statin 80 mg + Niacin Extended-release (ER)	Participants in Russia and Brasil will receive 80 mg Simvastatin + niacin. All other participants will receive 80 mg Atorvastatin + niacin
Statin 10 mg	Participants in Russia and Brasil will receive 10 mg Simvastatin. All other participants will receive 10 mg Atorvastatin.

Participant Flow: Overall Study

	Statin 80 mg + Niacin Extended-release (ER)	Statin 10 mg
STARTED	**50**	**50**
COMPLETED	**40**	**43**
NOT COMPLETED	**10**	**7**
Protocol Violation	**1**	**0**
Adverse Event	**8**	**5**
Withdrawal by Subject	**1**	**2**

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
Statin 80 mg + Niacin ER	Participants in Russia and Brasil will receive 80 mg Simvastatin + niacin. All other participants will receive 80 mg Atorvastatin + niacin.
Statin 10 mg	Participants in Russia and Brasil will receive 10 mg Simvastatin. All other participants will receive 10 mg Atorvastatin.
Total	Total of all reporting groups

Baseline Measures

	Statin 80 mg + Niacin ER	Statin 10 mg	Total
Number of Participants [units: participants]	**50**	**50**	**100**
Age [units: years] Mean (Standard Deviation)	**69.68 (9.42)**	**69.20 (8.63)**	**69.47 (8.99)**
Gender [units: participants]			
Female	**15**	**17**	**32**
Male	**35**	**33**	**68**

Outcome Measures

Hide All Outcome Measures

1. Primary: Composite Score of Plaque Inflammation/Stability Gene Expression as Assayed by Ribonucleic Acid (RNA) Taqman Analysis [Time Frame: At time of carotid endarterectomy (after 4 to 12 weeks of dosing)]

Measure Type	Primary
Measure Title	Composite Score of Plaque Inflammation/Stability Gene Expression as Assayed by Ribonucleic Acid (RNA) Taqman Analysis
Measure Description	Excised carotid plaques were evaluated for the gene expression of 60 biomarkers associated with inflammation ("Hot" biomarkers) & 25 biomarkers associated with stability ("Cold" biomarkers). Each biomarker was assayed using a quantitative polymerase chain reaction method and results were reported as a Cycle Threshold, (Ct). A Composite Score was calculated by averaging the Ct for each of the 25 "cold" genes, and subtracting the average Ct for the 60 "hot" genes. A higher composite score was associated with greater inflammation and a lower score was associated with stability (non-inflamed).
Time Frame	At time of carotid endarterectomy (after 4 to 12 weeks of dosing)
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.
Only participants who completed the study, had evaluable plaque samples and were at least 80% compliant with dosing schedule were included in the analysis.

Reporting Groups

	Description
Statin 80 mg + Niacin Extended-release (ER)	Participants in Russia and Brasil will receive 80 mg Simvastatin + niacin. All other participants will receive 80 mg Atorvastatin + niacin
Statin 10 mg	Participants in Russia and Brasil will receive 10 mg Simvastatin. All other participants will receive 10 mg Atorvastatin.

Measured Values

	Statin 80 mg + Niacin Extended-release (ER)	**Statin 10 mg**
Number of Participants Analyzed [units: participants]	**36**	**34**
Composite Score of Plaque Inflammation/Stability Gene Expression as Assayed by Ribonucleic Acid (RNA) Taqman Analysis [units: Cycle threshold (Ct)] Mean (Standard Deviation)	**1.36 (1.17)**	**0.82 (1.33)**

Statistical Analysis 1 for Composite Score of Plaque Inflammation/Stability Gene Expression as Assayed by Ribonucleic Acid (RNA) Taqman Analysis

Groups [1]	All groups
Method [2]	ANOVA

P Value [3]	0.811
Least Square Mean Difference [4]	0.27
90% Confidence Interval	-0.24 to 0.78

[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:
	No text entered.
[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.

2. Primary: Plaque Instability Protein Composite Score [Time Frame: At time of carotid endarterectomy (after 4 to 12 weeks of dosing)]

Measure Type	Primary
Measure Title	Plaque Instability Protein Composite Score
Measure Description	Each excised plaque was analyzed using an assay of 20 proteins that reflect plaque composition and inflammation. Each protein was assigned scaled signs, with a lower (negative) sign associated with plaque stability and a higher (positive) sign associated with plaque inflammation/instability. The Composite Score was the average amounts of all the 20 proteins with their associated signs. A higher Composite Score is associated with more plaque instability.
Time Frame	At time of carotid endarterectomy (after 4 to 12 weeks of dosing)
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.
Only participants who completed the study, had evaluable plaque samples and were at least 80% compliant with dosing schedule were included in the analysis.

Reporting Groups

	Description
Statin 80 mg + Niacin Extended-release (ER)	Participants in Russia and Brasil will receive 80 mg Simvastatin + niacin. All other participants will receive 80 mg Atorvastatin + niacin
Statin 10 mg	Participants in Russia and Brasil will receive 10 mg Simvastatin. All other participants will receive 10 mg Atorvastatin.

Measured Values

	Statin 80 mg + Niacin Extended-release (ER)	**Statin 10 mg**
Number of Participants Analyzed [units: participants]	**36**	**34**

Plaque Instability Protein Composite Score **[units: Score]** **Mean (Standard Deviation)**	**-7.19 (10.45)**	**-10.48 (11.70)**

Statistical Analysis 1 for Plaque Instability Protein Composite Score

Groups [1]	All groups
Method [2]	ANOVA
P Value [3]	0.898
Least Square Mean Difference [4]	3.64
90% Confidence Interval	-1.09 to 8.36

[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:
	No text entered.
[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.

3. Primary: Total Cholesterol and Free Cholesterol Measured by Enzymatic Chromogenic Assay [Time Frame: At time of carotid endarterectomy (after 4 to 12 weeks of dosing)]

Measure Type	Primary
Measure Title	Total Cholesterol and Free Cholesterol Measured by Enzymatic Chromogenic Assay
Measure Description	Cholesterol ester was to be calculated by the following formula: Cholesterol Ester = Total Cholesterol – Free Cholesterol.
Time Frame	At time of carotid endarterectomy (after 4 to 12 weeks of dosing)
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.
Only participants who completed the study, had evaluable plaque samples and were at least 80% compliant with dosing schedule were to be included in the analysis. This was not performed due to technical concerns. Instead, the cholesterol content determination, if performed, will use mass spectrometry approach and would be an exploratory objective.

Reporting Groups

	Description
Statin 80 mg + Niacin Extended-release (ER)	Participants in Russia and Brasil will receive 80 mg Simvastatin + niacin. All other participants

	will receive 80 mg Atorvastatin + niacin
Statin 10 mg	Participants in Russia and Brasil will receive 10 mg Simvastatin. All other participants will receive 10 mg Atorvastatin.

Measured Values

	Statin 80 mg + Niacin Extended-release (ER)	Statin 10 mg
Number of Participants Analyzed [units: participants]	**0**	**0**
Total Cholesterol and Free Cholesterol Measured by Enzymatic Chromogenic Assay		

No statistical analysis provided for Total Cholesterol and Free Cholesterol Measured by Enzymatic Chromogenic Assay

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	No text entered.
Additional Description	No text entered.

Reporting Groups

	Description
Statin 80 mg + Niacin Extended-release (ER)	Participants in Russia and Brasil will receive 80 mg Simvastatin + niacin. All other participants will recieve 80 mg Atorvastatin + niacin
Statin 10 mg	Participants in Russia and Brasil will receive 10 mg Simvastatin. All other participants will recieve 10 mg Atorvastatin.

Serious Adverse Events

	Statin 80 mg + Niacin Extended-release (ER)	Statin 10 mg
Total, serious adverse events		
# participants affected / at risk	**9/50 (18.00%)**	**7/50 (14.00%)**
Cardiac disorders		
Atrial Fibrillation † 1		
# participants affected / at risk	**1/50 (2.00%)**	**0/50 (0.00%)**
# events	**1**	**0**
Coronary Artery Occlusion † 1		
# participants affected / at risk	**1/50 (2.00%)**	**0/50 (0.00%)**
# events	**1**	**0**
Myocardial Infarction † 1		
# participants affected / at risk	**1/50 (2.00%)**	**1/50 (2.00%)**

# events	1	1
Eye disorders		
Glaucoma † 1		
# participants affected / at risk	1/50 (2.00%)	0/50 (0.00%)
# events	1	0
Gastrointestinal disorders		
Gastritis † 1		
# participants affected / at risk	1/50 (2.00%)	0/50 (0.00%)
# events	1	0
General disorders		
Chest Pain † 1		
# participants affected / at risk	0/50 (0.00%)	1/50 (2.00%)
# events	0	1
Infections and infestations		
Bronchitis † 1		
# participants affected / at risk	0/50 (0.00%)	1/50 (2.00%)
# events	0	1
Pyelonephritis Chronic † 1		
# participants affected / at risk	0/50 (0.00%)	1/50 (2.00%)
# events	0	1
Injury, poisoning and procedural complications		
Fall † 1		
# participants affected / at risk	1/50 (2.00%)	0/50 (0.00%)
# events	1	0
Overdose † 1		
# participants affected / at risk	1/50 (2.00%)	0/50 (0.00%)
# events	1	0
Pelvic Fracture † 1		
# participants affected / at risk	0/50 (0.00%)	1/50 (2.00%)
# events	0	1
Musculoskeletal and connective tissue disorders		
Rhabdomyolysis † 1		
# participants affected / at risk	1/50 (2.00%)	0/50 (0.00%)
# events	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Gastric Cancer † 1		
# participants affected / at risk	0/50 (0.00%)	1/50 (2.00%)
# events	0	1
Myelofibrosis † 1		
# participants affected / at risk	0/50 (0.00%)	1/50 (2.00%)
# events	0	1
Nervous system disorders		
Cerebrovascular Accident † 1		

# participants affected / at risk	**1/50 (2.00%)**	**0/50 (0.00%)**
# events	**1**	**0**

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA (14.0)

Other Adverse Events

Hide Other Adverse Events

Time Frame	No text entered.
Additional Description	No text entered.

Frequency Threshold

Threshold above which other adverse events are reported	5%

Reporting Groups

	Description
Statin 80 mg + Niacin Extended-release (ER)	Participants in Russia and Brasil will receive 80 mg Simvastatin + niacin. All other participants will recieve 80 mg Atorvastatin + niacin
Statin 10 mg	Participants in Russia and Brasil will receive 10 mg Simvastatin. All other participants will recieve 10 mg Atorvastatin.

Other Adverse Events

	Statin 80 mg + Niacin Extended-release (ER)	**Statin 10 mg**
Total, other (not including serious) adverse events		
# participants affected / at risk	**5/50 (10.00%)**	**2/50 (4.00%)**
Vascular disorders		
Flushing † 1		
# participants affected / at risk	**5/50 (10.00%)**	**2/50 (4.00%)**
# events	**5**	**2**

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA (14.0)

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:** Publications derived from the study should include input from the investigator(s) and SPONSOR. After to the multicenter publication, or 24 months after completion of the study, whichever comes first, an investigator may publish the results for the study site independently. The SPONSOR must have the opportunity to review all proposed publications 60 days prior to submission for publication/presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission.

Results Point of Contact:

Name/Title: Senior Vice President, Global Clinical Development
Organization: Merck Sharp & Dohme Corp
phone: 1-800-672-6372
e-mail: ClinicalTrialsDisclosure@merck.com

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ClinicalTrials.gov Identifier:	NCT00804843 History of Changes
Other Study ID Numbers:	0000-111 2008_598 (Other Identifier: Merck Study Number)
Study First Received:	December 8, 2008
Results First Received:	December 21, 2011
Last Updated:	September 28, 2015
Health Authority:	United States: Food and Drug Administration

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