

IMPROVE-IT

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Sponsor:

Schering-Plough Research

Study Purpose:

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs. Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome (**IM**Proved **R**eduction of **O**utcomes: **V**ytorin **E**fficacy **I**nternational Trial - **IM**PROVE IT)

Objective:

The intent of this clinical study is to demonstrate such benefit of Ezetimibe/Simvastatin Combination over at least 4-5 years of follow up in high risk coronary artery disease subjects beyond known benefits of Simvastatin Monotherapy.

Inclusion:

1. *Clinically stable* subject within *10 days* of hospital presentation following NSTEMI-ACS defined as
 - a) NSTEMI-ACS subject participating in EARLY-ACS study and does not undergo CABG
 - b) NSTEMI-ACS with the following criteria
 1. Symptoms of ischemia ≥ 10 min at rest
 2. ≥ 50 years of age
 3. At least one of the following:
 - New ST-T or transient STE ≥ 0.1 mV (2 contiguous leads)
 - CKMB or Trop I or Trop T $>$ ULN (2 contiguous leads)
 - Diabetes Mellitus
 - Any history of prior MI or CABG ≥ 3 years prior
 - History of peripheral arterial disease
 - History of cerebrovascular disease

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- Multivessel CAD with ≥ 2 vessels with $\geq 50\%$ stenosis
- 2. LDL-C and cholesterol criteria at time of admission (as soon as possible after presentation and no later than 24 hours)
 - a) Statin *naïve*: No statin therapy 4 weeks prior or started statin ≤ 7 days earlier or during index hospitalization
 - 1. All other subjects (including those who initiate prescription lipid-lowering therapy after the qualifying ACS hospital admission) are considered to be "lipid-therapy naïve"
 - 2. To be eligible, a subject receiving chronic prescription lipid-lowering therapy must be receiving therapy with a lipid-lowering potency equal to or less than simvastatin 40 mg QD
 - b) *Chronic*: A subject receiving chronic lipid-lowering therapy with LDL-C lowering potency greater than simvastatin 40 mg will not be eligible. The prohibited chronic lipid-lowering therapies are the following:
 - 1. All doses of simvastatin >40 mg;
 - 2. All doses of atorvastatin ≥ 40 mg;
 - 3. All doses of rosuvastatin;
 - 4. All doses of Ezetimibe/Simvastatin Combination;
 - 5. Ezetimibe coadministered with any dose of any statin.-All other chronic prescription lipid lowering therapies will be considered equal or less potent than simvastatin 40 mg QD and subjects taking such therapies may be considered for enrollment.
 - c) A lipid-therapy naïve subject will be eligible to enroll if his/her LDL-C concentration is ≥ 50 mg/dL and ≤ 125 mg/dL
 - d) Chronic prescription lipid-lowering therapy will be eligible to enroll, if his/her LDL-C concentration is >50 mg/dL and <100 mg/dL
 - e) The following conditions concerning lipid concentrations and experience with chronic prescription lipid-lowering therapy:
 - 1. Blood lipid levels, including LDL-C, should be measured as close as possible to each subject's presentation to a hospital, but no later than 24 hours after admission.
 - 2. The specimens do not need to be obtained after fasting.
 - 3. If a recent lipid panel (<6 months prior to presentation) is available, the values may be used for subject screening and determination of eligibility.
 - 4. If only a TC level is available at the time of admission, the subject will still be eligible if TC concentrations meet the following criteria at the time of admission and repeat fasting lipid measurements obtained as soon as possible.
 - TC concentration ≤ 190 mg/dL for a lipid-therapy naïve subject;

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- TC concentration ≤ 150 mg/dL for a subject receiving chronic prescription lipid-lowering therapy.
- f) Subject must have a plasma triglyceride level ≤ 350 mg/dL. A subject found to have a non-fasting TG > 350 mg/dL upon admittance into a hospital, but have TG < 1500 mg/dL, must have TG ≤ 350 mg/dL on a fasting specimen obtained as soon as possible.
- 3. Women of child bearing potential must use medically accepted contraception during study period and 6 weeks afterwards. All postmenarchal women who are < 2 years menopausal or who have not had surgical sterilization or a hysterectomy are considered to be women of childbearing potential.

Exclusion:

- Clinically unstable 24 hours prior to randomization including hypotension, pulmonary edema, acute MR, acute VSD, recurrent ischemia, recent CVA, VF, sustained VT, high grade heart block
- Current statin rx with greater potency than simvastatin 40mg (atorvastatin 40-80 mg, all doses of rosuvastatin or all doses of ezetimibe/simvastatin combination)
- Discontinuation of existing lipid lowering regimen poses increased risk to the subject
- Allergy/sensitivity to any statin or ezetimibe
- Active liver disease or persistent unexplained serum transaminases $\geq 2x$ ULN
- History of alcohol and /or drug abuse
- Pregnant or lactating woman or intentions to become pregnant
- Use of prohibited meds including probucol, amiodarone, cyclosporine, fibrates, resins, niacin (> 100 mg/day), danazol, antifungal azoles, macrolide/ketolide antibiotics, protease inhibitors, nefazodone, diltiazem, verapamil, grapefruit juice > 1 quart/day, statins, ezetimibe, fusidic acid, torcetrapib (within 1 year prior to Screening/Randomization) or any investigational drugs
- Creatinine clearance < 30 mL/min or dialysis within 30 days
- Any investigational drug use within 30 days of screening
- Participation in any other clinical study involving investigational drug or device other than EARLY ACS trial within the last 30 days
- Prior enrollment in IMPROVE-IT
- Subject is part of staff personnel directly involved with study or a family member of investigational study staff
- Any clinically significant condition that in the investigator's opinion would interfere with study evaluation or participation

Status:

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Follow-up ONLY!

If you have any questions, please feel free to contact the coordinators, and they will be happy to answer any questions you have regarding this study.