FOURIER STUDY

Did the study achieve its main objective?  

**YES**

**FOURIER compared Repatha® with placebo in patients who were taking a statin and had hardening or narrowing of the arteries and a normal to high LDL cholesterol level.**

This study compared two groups of patients. 1) Patients taking Repatha® (evolocumab) plus a standard cholesterol-lowering medication (statin) Lipitor® (atorvastatin); 2) patients taking placebo plus Lipitor®.

The main objective of the FOURIER study was to find out whether Repatha® (when used in addition to a statin) would reduce the risk of serious heart disease events and stroke including: death caused by heart disease, heart attack, stroke, hospitalization for chest pain due to poor blood flow (angina), coronary artery bypass or heart artery stent. The study included patients who were taking Lipitor® or Liptor® plus Zetia® (ezetimibe) and who had hardening or narrowing of the arteries and a normal to high level of LDL (bad cholesterol; 70 mg per deciliter or greater).

Results after 48 weeks showed that Repatha® significantly reduced the occurrence of serious heart disease events and stroke. Serious heart disease events and stroke occurred in 9.8% of patients taking Repatha® compared with 11.3% of patients taking placebo.

Repatha® was safe and effective in the population that was studied: The study results show that Repatha® is safe and that patients who have hardening of the arteries may benefit from adding Repatha® to their current cholesterol-lowering medications.

Did Repatha® increase the risk of side-effects?  

**NO**

The rate of the most common side-effects associated with cholesterol medications (muscle-weakeness and elevated liver tests) was low and there was no significant difference between the Repatha® group and the placebo group. Repatha® did not increase any of the common side-effects most often associated with statins, including memory loss, thinking, or cataracts. Injection-site reactions were uncommon, but they were more frequent with Repatha® (2.1% versus 1.6%).

The rates of allergic reactions also did not differ significantly between the groups (3.1% for Repatha® versus 2.9% for placebo).
How was the FOURIER study designed?

**Clinical studies** are conducted in a series of steps called phases. Each phase is designed to answer a separate research question. In most cases, medications go through three phases before the medication is approved with an additional phase being conducted after it is approved to confirm its effectiveness and side-effects with long-term use.

A **Phase 3** study is a study in which the medication is given to a large group of people to confirm its effectiveness, monitor side-effects, compare it with commonly used medications (or a placebo), and collect information that will allow the medication to be used safely. FOURIER was a Phase 3 study, in this study patients were selected by chance to receive Repatha® by injection or placebo (inactive liquid) by injection.

**Why was the study done:** Low-density lipoprotein (LDL) or bad cholesterol is a well-known and controllable risk factor for heart disease. Repatha® (generic name: evolocumab) belongs to a new class of medications that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9), a protein that is naturally produced by the body. Previous studies have shown that inhibiting PCSK9 can reduce the level of LDL in the blood by 60%. It was not known if this would lead to fewer heart events and stroke.

Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) was a Phase 3 study designed to measure the ability of Repatha to not only lower bad cholesterol but also to determine if taking Repatha in combination with high-to-moderate intensity statin medication could reduce the risk of serious heart disease or stroke in patients with hardening or narrowing of the arteries (atherosclerosis) who were at increased risk for serious and life-threatening heart conditions and stroke. Over 1 million people in the United States have a heart attack or a threatened heart attack each year. According to the American Heart Association nearly 500,000 Americans die from atherosclerosis each year.

**Who was studied:** The FOURIER study included people who were at increased risk of a serious heart disease event, stroke or other vascular disease due to hardening or narrowing of the arteries (atherosclerotic disease); meaning the patient had to have had a heart attack, stroke, and/or symptomatic narrowing of the arteries going to the limbs (peripheral artery disease).

Patients also had to have a fasting LDL level of 70 mg per deciliter or higher. Study participants included people between the ages of 40 and 85 years who were taking a cholesterol-lowering medication, preferably a high-intensity statin. All patients had to be taking at least 20 mg per day of Lipitor® or a comparable dose of a similar statin with or without Zetia®.
How was the study designed: FOURIER was a Phase 3 study, conducted from February 2013 through June 2015. The study was conducted at 1,242 centers in 49 countries (see page X) and included 27,564 patients. Patients were selected by chance to be included in one of two study groups in a one-to-one ratio:
- Group 1: patients treated with Repatha (13,784)
- Group 2: patients treated with a placebo (13,780)

This was a double-blind study, meaning that neither the patients nor their doctors knew which medication the patients were going to receive. Patients in Group 1 received Repatha® in either a 140 mg dose every 2 weeks or a 420 mg dose every month according to their personal preference for frequency and size of the injection. Group 2 received the same doses of placebo according to their personal preference for frequency and size of the injection. Repatha® was compared with placebo because there is no standard medication to use for comparison.

What were the characteristics of study participants: Patients in the study were an average age of 63 years and more were male (75.4%). They were also more likely than the general population to have had a serious heart condition associated with high cholesterol and hardening of the arteries (see graph).

As the study was intended to measure how well Repatha® worked in patients who had a normal or high LDL level, almost all of the participants were taking either a high- or moderate-intensity statin medication at the start of the study; 5.2% were also taking Zetia® to control their cholesterol. Many patients were also taking preventive medications associated with other heart and vascular diseases such as stroke and high blood pressure (see graph).
How was the FOURIER study designed?

Phase 3

The Percentage of Participants Who Were Taking Heart and Vascular Disease Medications at the Start of the Study:

- **Cholesterol**
  - High-intensity statins: 69.3%
  - Moderate-intensity statins: 30.4%

- **Other Atherosclerosis Treatments**
  - Aspirin or other anti-clotting agent: 92.3%
  - Beta-blockers: 75.6%
  - ACE or ARB: 78.2%

What else was learned from FOURIER: Patients who have hardening of the arteries could benefit from adding Repatha® to their current cholesterol-lowering medications because of its ability to lower LDL. In the study, Repatha® reduced LDL levels by 59% (to 30 mg per deciliter). In addition to lowering LDL, Repatha® provided additional heart disease benefit, and the benefits of Repatha® increased over time.

The study data also suggests that Repatha® may be even more beneficial in preventing heart attacks, stroke, and death from other heart conditions over time. The reduction in the incidence of heart attack and stroke increased from 12% in the first year to 19% in the second year.

What comes next: FOURIER clearly showed that patients with hardening of the arteries who are currently taking statin medications would get additional benefit from taking Repatha®. However, the study period was short and the study did not show whether or not the addition of Repatha® prevents death from heart disease – a longer study would need to test this.

Also, other studies measuring the benefits and risks of Repatha® for other lower-risk groups, and the benefits of starting Repatha® immediately after a serious heart event are needed.
FOURIER study general Information

Full title: Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER)

Clinical trial number: NCT01764633 first listed on ClinicalTrials.gov on January 8, 2013 link: https://clinicaltrials.gov/show/NCT01764633

Study presentation and publication:
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Published in:
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Sponsor: Amgen, One Amgen Center Dr, Thousand Oaks, CA 91320-1799 USA
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FOURIER was conducted in 1,242 medical centers in 49 countries. Location of participants: Europe 60%, US 20%, all other 20%

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