### Background and Overview

**Background**
- High low-density lipoprotein cholesterol (LDL-C) is a long-established, modifiable risk factor for cardiovascular disease (CVD).
- Statins have been extensively used in the past, not only for their cholesterol reduction capabilities, but also for their cardiovascular benefit.
  - Many patients are unable/unwilling to take statins because of the possibility of myalgias, which severely limits their maximal use in patients that may greatly benefit.
- Previous studies:
  - PROVE IT-TIMI 22 and TNT
    - Suggested that aiming for LDL-C targets led to significant reductions in major cardiovascular events
    - Showed that more intensive statin regimens lowered LDL-C from 100 mg/dL to 70 mg/dL
  - IMPROVE-IT
    - Lowered LDL-C from 70 mg/dL to 54 mg/dL and showed significantly reduced cardiovascular events
  - GLAGOV
    - Showed that continued CV benefit can be seen as LDL-C is reduced even to 20-25 mg/dL
- Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors are an emerging class of medications that have been shown to decrease LDL-C levels by 60%.
  - The LDL receptor binds LDL-C in the circulation and transports it into the cell, out of the bloodstream. Once this is complete, the receptor cycles back to the membrane to repeat this process.
  - When PCSK9 is bound to the LDL receptor, the receptor is not recycled after delivering the LDL-C into the cell, and cannot return to the cell membrane.
  - Thus, inhibiting PCSK9 would allow more of the receptors to be recycled, providing greater reductions in circulating LDL.
- In the past, marginal CV benefit has been shown when adding additional lipid-lowering therapies to statins. However, none of the other classes tested with a background of statin therapy has shown the potential to have as profound an effect on LDL-C as PCSK9 inhibitors.

**Objective**
To test the clinical efficacy and safety of evolocumab when added to high-intensity or moderate-intensity statin therapy in patients with clinically evident atherosclerotic cardiovascular disease.

**Methods**

**Study Design**
Randomized, double-blind, placebo-controlled, multinational clinical trial

**Funding**
Amgen pharmaceuticals

**Inclusion Criteria**
- Adults age 40-85
- History of clinically-evident cardiovascular disease (MI, non-hemorrhagic stroke, systemic PAD)
- At least 1 major or 2 minor risk factors:
  - **Major**
    - Diabetes (type 1 or 2)
    - Age 65-85
    - MI or non-hemorrhagic stroke within 6 months of screening
    - Additional diagnosis of MI or non-hemorrhagic stroke, excluding qualifying event
    - Current daily cigarette smoking
    - History of symptomatic PAD
  - **Minor**
    - History of non-MI-related coronary revascularization
    - Residual CAD with ≥40% stenosis in ≥2 large vessels
    - Most recent HDL-C <40 mg/dL (men) and <50 mg/dL (women)
    - Most recent hsCRP >2.0 mg/dL
    - Most recent LDL-C ≥130 mg/dL or non-HDL-C ≥160 mg/dL
    - Metabolic syndrome
    - Most recent fasting LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL during screening after ≥2 weeks of stable lipid lowering therapy
### Exclusion Criteria
- MI or stroke within 4 weeks of randomization
- NYHA class III or IV, or last known LVEF <30%
- Known hemorrhagic stroke at any time
- Uncontrolled tachycardia
- Planned or expected cardiac surgery or revascularization within 3 months after randomization
- Uncontrolled HTN
- Use of CETP inhibition treatment, mipomersen, or lomitapide within 12 months prior to randomization. Fenofibrate therapy must be stable for at least 6 weeks prior to final screening at a dose that is appropriate for the duration of the study in the judgement of the investigator. Other fibrate therapies are prohibited.
- Prior use of PCSK9 inhibition treatment other than evolocumab or use of evolocumab <12 weeks prior to final lipid screening
- Untreated or inadequately treated hyperthyroidism or hypothyroidism
- Active liver disease or hepatic dysfunction
- Recipient of any major organ transplant
- LDL or plasma apheresis within 12 months prior to randomization
- Severe, concomitant non-cardiovascular disease that is expected to reduce life expectancy to < 3 years
- CK >5 times the ULN at final screening
- Known major active infection or major hematologic, renal, metabolic, GI, or endocrine dysfunction
- Malignancy within the last 10 years
- Received systemic drugs that have known major interactions with background statin therapy within 1 month prior to randomization
- Currently or recently enrolled in another investigational drug/device study
- Females of childbearing potential who have used or are not willing to use acceptable methods of birth control, or who are currently or soon-to-be pregnant/breastfeeding

### Interventions
- Patients were assigned 1:1 to receive either evolocumab or placebo
  - Patients were then allowed to choose between 140 mg every 2 weeks or 420 mg monthly evolocumab or matching placebo
- Groups were stratified according to final screening LDL-C, and region

### Outcome Measures
- Primary endpoint – Composite of: cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization
- Secondary endpoint – Composite of: cardiovascular death, MI, or stroke

### Statistical Analysis
- Primary analysis was based on the time from randomized study-group assignment to the first occurrence of any element of the primary composite endpoint
- If the primary endpoint achieved significance, then it would be tested against the secondary endpoint
- Conducted based on an intention-to-treat basis
- Safety evaluations included any patient who had received a single dose of study agent, and for whom post-dose data were available
- Based on secondary endpoint, 1630 events would be required to provide 90% power to detect a 15% relative risk reduction

### Results

#### Baseline Characteristics
- 27,564 total patients
  - Evolocumab: 13,784
  - Placebo: 13,780
- The two groups were very well matched
- Patients were primarily male and average age was 63 years
- The majority of included patients had a history of MI
- Nearly 70% of patients were taking a high-intensity statin, as recommended

#### LDL
- At baseline, median LDL-C was 92 mg/dL
  - Mean absolute LDL-C reduction of 56 mg/dL
  - This reduction was maintained over time
    - At 48 weeks, 87% of patients had LDL-C <70 mg/dL
Efficacy Endpoints

- Primary endpoint occurrence
  - Evolocumab: 1344 patients (9.8%)
  - Placebo: 1563 patients (11.3%)
  - HR, 0.85; 95% CI, 0.79 to 0.92; p<0.001
- Secondary endpoint occurrence
  - Evolocumab: 816 patients (5.9%)
  - Placebo: 1013 patients (7.4%)
- Risk reduction continued to increase over time
- The benefits were consistent across all quartiles of baseline LDL-C levels
- The benefits were consistent, regardless of intensity of statin therapy, regardless of ezetimibe therapy, and with both the bi-weekly and monthly dosing regimens.

Safety Endpoints

- No significant between-group differences in:
  - Overall rates of adverse events
  - Serious adverse events
  - Adverse events thought to be related to the study agent and leading to discontinuation of the study regimen
- Injection site reactions were rare, but more frequent with evolocumab (2.1% vs. 1.6% placebo)

Conclusions and Discussion

- The addition of evolocumab to statin therapy significantly reduced the risk of CV events
- The translation of reductions in LDL-C levels into cardiovascular clinical benefit requires time
- 74 patients would need to be treated over a period of 2 years to prevent a CV death, MI, or stroke
- The magnitude of benefit of evolocumab in reducing the risk of major coronary events, stroke, and urgent coronary revascularization is largely consistent with the benefit seen with statins
- Limitations
  - Relatively short duration of follow-up may limit the number of adverse events

Application

- In the absence of guideline recommendations, this medication is reasonable to add in patients who would benefit from additional lipid lowering therapy.
- This medication can also be considered in patients unwilling or unable to take statins.
- Price will likely limit use for now.

References