Evolocumab (AMG 145) Fact Sheet
Investigational Product

Overview

Evolocumab (AMG 145) is an investigational fully human monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein that targets low density lipoprotein (LDL) receptors for degradation and thereby reduces the liver’s ability to remove LDL cholesterol (LDL-C), or “bad” cholesterol, from the blood.1

PROFICIO, which stands for the Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations, is a large and comprehensive clinical trial program evaluating evolocumab in 20 clinical trials, with a combined planned enrollment of nearly 30,000 patients.

The Phase 3 program includes 14 trials to evaluate evolocumab administered every two weeks and monthly in multiple patient populations, including in combination with statins in patients with hyperlipidemia (LAPLACE-2 and YUKAWA-2); in patients with hyperlipidemia who cannot tolerate statins (GAUSS-2 and GAUSS-3); as a stand-alone treatment in patients with hyperlipidemia (MENDEL-2); in patients whose elevated cholesterol is caused by genetic disorders called heterozygous (RUTHERFORD-2 and TAUSSIG) and homozygous (TESLA and TAUSSIG) familial hypercholesterolemia; as well as the administration of evolocumab (THOMAS-1 and THOMAS-2).2

Five studies in the evolocumab Phase 3 program will provide long-term safety and efficacy data. These include FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk), which will assess whether treatment with evolocumab in combination with statin therapy compared to placebo and statin therapy reduces recurrent cardiovascular events in approximately 22,500 patients with cardiovascular disease; DESCARTES (Durable Effect of PCSK9 Antibody Compared with Placebo Study) in patients with hyperlipidemia at risk for cardiovascular disease; OSLER-2 (Open Label Study of Long Term Evaluation Against LDL-C Trial-2) in patients with high cholesterol who completed any of the Phase 3 studies; GLAGOV (Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound), which will determine the effect of evolocumab on coronary atherosclerosis in approximately 950 patients undergoing cardiac catheterization; and TAUSSIG (Trial Assessing Long Term Use of PCSK9 Inhibition in Subjects with Genetic LDL Disorders), which will assess the long-term safety and efficacy of evolocumab on LDL-C in patients with severe familial hypercholesterolemia.3-7

The effect on outcomes has not been established.

Hypercholesterolemia, or high cholesterol, is a major public health issue in most countries as it contributes to the risk of developing cardiovascular disease, the leading cause of death among men and women.8,9 Treatment of high cholesterol is aimed at lowering a patient’s LDL-C to reduce their risk of cardiovascular events, like heart attacks and strokes.8,10 According to the Centers for Disease Control and Prevention, more than 71 million American adults have high LDL-C.11 While statins are effective in reducing LDL-C levels and treatment with evolocumab in combination with statin therapy reduces recurrent cardiovascular events in approximately 22,500 patients with cardiovascular disease who are on statin therapy Co-primary Endpoints: Percent change from baseline in LDL-C after 12 weeks of treatment; mean percent change from baseline in LDL-C after 10 and 12 weeks of treatment N = 1,896

RUTHERFORD-2 (Phase 3: NCT01763918)
Population: Patients with heterozygous familial hypercholesterolemia, a genetic disorder that causes high cholesterol Co-primary Endpoints: Percent change from baseline in LDL-C after 12 weeks of treatment; mean percent change from baseline in LDL-C after 10 and 12 weeks of treatment N = 329

TESLA (Phase 2/3: NCT01588496)
Population: Patients with homozygous familial hypercholesterolemia, a rare genetic disorder that causes high cholesterol
Primary Endpoint: Percent change from baseline in LDL-C after 12 weeks of treatment
N = 49

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on the surface of the liver increase, allowing for more removal of LDL-C from the blood and lower levels of LDL-C.1,14

**Hypothized Mechanism of Action**
Evolocumab, being developed by Amgen scientists, is an investigational fully human monoclonal antibody designed to bind to PCSK9 and inhibit PCSK9 from binding to LDL receptors on the liver surface.1 In the absence of PCSK9, there are more LDL receptors on the surface of the liver to remove LDL-C from the blood.14

**Results of Interest**
Click on the links below to view the press releases: Amgen Announces Positive Top-Line Results From Phase 3 TESLA Trial Of Evolocumab (AMG 145) In Patients With Homozygous Familial Hypercholesterolemia (Amgen press release, 3/17/14)

<table>
<thead>
<tr>
<th>Study</th>
<th>Target Enrollment</th>
<th>Population</th>
<th>Primary Endpoint</th>
<th>Final Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TESLA</td>
<td>3,515</td>
<td>Patients with hyperlipidemia and a wide range of cardiovascular risk</td>
<td>Change from baseline in LDL-C after 52 weeks of treatment</td>
<td>N = 901</td>
</tr>
<tr>
<td>RUTHERFORD-2</td>
<td>950</td>
<td>Patients with genetic causes of high LDL-C (e.g., mutations in LDL receptor or PCSK9)</td>
<td>Incidence of adverse events</td>
<td>Target Enrollment: 250</td>
</tr>
<tr>
<td>LAPLACE-TIMI 57</td>
<td>901</td>
<td>Patients with hypercholesterolemia and a wide range of cardiovascular risk</td>
<td>Incidence of adverse events</td>
<td>N = 901</td>
</tr>
<tr>
<td>MENDEL</td>
<td>1,700</td>
<td>Patients with mixed dyslipidemia who completed a qualifying treatment</td>
<td>Percent change from baseline in LDL-C after 52 weeks of treatment</td>
<td>N = 901</td>
</tr>
<tr>
<td>TAUSSIG</td>
<td>22,500</td>
<td>Patients at high risk for cardiovascular disease who are on effective statin therapy</td>
<td>Time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization, whichever occurs first</td>
<td>Target Enrollment: 22,500</td>
</tr>
<tr>
<td>DESCARTES</td>
<td>3,500</td>
<td>Patients with high cholesterol and a wide range of cardiovascular risk</td>
<td>Incidence of adverse events</td>
<td>Target Enrollment: 250</td>
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</tbody>
</table>

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**Additional Information**
For further information, visit www.amgen.com.

**Forward-Looking Statements**
This Fact Sheet contains forward-looking statements that are based on Amgen’s current expectations and beliefs and are subject to a number of risks, uncertainties, and assumptions that could cause actual results to differ materially from those described. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including those related to: expected clinical or regulatory results or practices; development of Amgen’s product candidates, including anticipated regulatory filings; and current scientific theories and research regarding the diseases or conditions targeted by the product candidates. Forward-looking statements involve significant risks and uncertainties, including those described in the most recent Annual Report on Form 10-K and any subsequent periodic reports on Form 10-Q and Form 8-K filed by Amgen with the U.S. Securities and Exchange Commission, and actual results may vary materially. Except where otherwise indicated, Amgen is providing this information as of March 18, 2014, and at the time of the issuance of this Fact Sheet.
does not undertake any obligation to update any forward-looking statements contained in this Fact Sheet as a result of new information, future events, or otherwise.

References
1 Amgen data on file, Investigator Brochure.

GAUSS-3
(Phase 3: NCT01984424)
Population: Patients who cannot tolerate statin therapy
Co-primary Endpoints: Percent change from baseline in LDL-C after 24 weeks of treatment; mean percent change from baseline in LDL-C after 22 and 24 weeks of treatment
Target Enrollment = 500

THOMAS-1
(Phase 3: NCT01849497)
Population: Patients with primary hypercholesterolemia or mixed dyslipidemia
Primary Endpoint: Combination of subject reported outcomes across two attempted full-dose administrations at two and four weeks
Target Enrollment: 149

THOMAS-2
(Phase 3: NCT01879319)
Population: Patients with hypercholesterolemia or mixed dyslipidemia
Primary Endpoint: Combination of subject reported outcomes across two attempted full-dose administrations at four and eight weeks
Target Enrollment: 164