# *PROFICIO: The Evolocumab Clinical Trial Program*

## *Backgrounder*

## *Program Overview*

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, an investigational fully human monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein that reduces the liver's ability to remove low-density lipoprotein cholesterol (LDL-C), or "bad" cholesterol, from the blood.[1] PROFICIO includes 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: LDL-C Assessment with PCSK9 MonoclonaL Antibody Inhibition Combined With Statin ThErapy-2 and YUKAWA-2: StudY of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk)[2]
- In patients with hyperlipidemia who cannot tolerate statins (GAUSS-2/GAUSS-3: Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects -2/3)[2]
- As a stand-alone treatment in patients with hyperlipidemia (MENDEL-2: Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2)[2]
- In patients whose elevated cholesterol is caused by a genetic disorder called heterozygous familial hypercholesterolemia (RUTHERFORD-2: RedUction of LDL-C With PCSK9 InhibiTion in HEteRozygous Familial HyperchOlesteRolemia Disorder Study-2 and TAUSSIG: Trial Assessing Long Term USe of PCSK9 Inhibition in Subjects WIth Genetic LDL Disorders)[2]
- In patients whose elevated cholesterol is caused by a genetic disorder called homozygous familial hypercholesterolemia (TESLA: Trial Evaluating PCSK9 Antibody in Subjects With LDL Receptor Abnormalities and TAUSSIG)[2]
- The administration of evolocumab (THOMAS-1 and THOMAS-2: THOMAS: Trial for HOMe-use of prefilled Auto-injector pen and 3.5 mL Personal Injector in AMG 145 administrationS)[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]

## *Program Design*

PROFICIO was designed to evaluate evolocumab every two weeks and monthly across a range of patient populations at risk for CVD who are unable to control their LDL-C despite currently available therapies. Based on the data seen to date, both dosing frequencies have comparable LDL-C reduction and the every two weeks or monthly dosing options of evolocumab may offer patients a choice on their treatment regimen.

The primary endpoint for the majority of pivotal lipid-lowering studies in the PROFICIO Phase 3 program is the percentage change from baseline in LDL-C at week 12 and mean percentage change from baseline in LDL-C at weeks 10 and 12.

The Phase 3 clinical trials are also evaluating changes in other lipid parameters, including triglycerides, lipoprotein(a) and high-density lipoprotein cholesterol (HDL-C).[2] The effect on outcomes is being evaluated and as such has not been established .

Additional information about clinical trials of evolocumab can be found at www.clinicaltrials.gov.

## *Phase 3 Study Results of Interest*

To view press releases on Phase 3 results released to date, click on the links below.

- Amgen Announces Positive Top-Line Results From Phase 3 TESLA Trial Of Evolocumab (AMG 145) In Patients With Homozygous Familial Hypercholesterolemia (Amgen press release, 03/17/14)
- Amgen Announces Positive Top-Line Results From Phase 3 RUTHERFORD-2 Trial Of Evolocumab (AMG 145) In Patients With Heterozygous Familial Hypercholesterolemia (Amgen press release, 1/30/14)
- Amgen Announces Positive Top-Line Results From Phase 3 LAPLACE-2 Trial Of Evolocumab (AMG 145) In Combination With Statins In Patients With High Cholesterol (Amgen press release, 1/28/14)
- Amgen Announces Positive Top-Line Results From Phase 3 GAUSS-2 Trial Of Evolocumab (AMG 145) In Statin Intolerant Patients With High Cholesterol (Amgen press release, 1/23/14)
- Amgen Announces Positive Top-Line Results From 52-Week Phase 3 DESCARTES Study of Evolocumab (AMG 145) in Patients With High Cholesterol (Amgen press release, 12/19/13)
- Amgen Announces Positive Top-Line Results From Phase 3 MENDEL-2 Trial of Evolocumab (AMG 145) in Patients With High Cholesterol (Amgen press release, 12/17/13)

# *PROFICIO Phase 3 Clinical Trial Program Overview*

Click on the links below to view the selected ongoing study summaries on www.clinicaltrials.gov.

## Patients with Genetic Causes of High LDL-C

### 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

### taussig

(Phase 2/3: NCT01624142)
Population: Patients with genetic causes of high LDL-C (e.g., mutations in LDL receptor or PCSK9)
Primary Endpoint: Incidence of adverse events
Target Enrollment = 250

### 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 = 58

## Secondary Prevention Study

### fourier

(Phase 3: NCT01764633)
Population: Patients at high risk for CVD who are on effective statin therapy
Primary Endpoint: Time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization, whichever occurs first
Target Enrollment = 22,500

## Patients with Atherosclerosis

### glagov

(Phase 3: NCT01813422)
Population: Patients with coronary artery disease taking lipid lowering therapy and undergoing coronary catheterization
Primary Endpoint: Change from baseline in percent atheroma volume (PAV) after 78 weeks of treatment
Target Enrollment = 950

### yukawa

(Phase 3: NCT01953328)
Population: Japanese patients at high risk for CVD 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 = 409

## Long-Term Safety and Efficacy Study

### descartes

(Phase 3: NCT01516879)
Population: Patients with hypercholesterolemia and a wide range of cardiovascular risk
Primary Endpoint: Percent change from baseline in LDL-C after 52 weeks of treatment
N = 901

## Combination Therapy Study

### laplace-2

(Phase 3: NCT01763866)
Population: Patients at risk for CVD 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

## Open-Label Extension Study

### osler-2

(Phase 3: NCT01854918)
Population: Patients with hyperlipidemia and mixed dyslipidemia who completed a qualifying evolocumab parent study
Primary Endpoint: Incidence of adverse events
[Time Frame: 104 weeks ]
Target Enrollment = 3,515

## Monotherapy Study

### mendel-2

(Phase 3: NCT01763827)
Population: Patients who are not taking a statin
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 = 614

## Patients with Statin Intolerance

### gauss-2

(Phase 3: NCT01763905)
Population: Patients who cannot tolerate 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 = 307

### 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
N (Part A)= 500
N (Part B)= 100

## Device Studies

**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
N = 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
N = 164

AMGEN

## Media Inquiries

Wendy Woods Williams, +1 (805) 341-5797, wwoodswi@amgen.com

## 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 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.
[2] Clinicaltrials.gov website: http://clinicaltrials.gov/ct2/results?term=%22evolocumab%22+and+%22phase+3%22&Search=Search. Accessed February 2014.
[3] Clinicaltrials.gov website: http://clinicaltrials.gov/ct2/show/NCT01764633. Accessed February 2014.
[4] Clinicaltrials.gov website: http://clinicaltrials.gov/ct2/show/NCT01624142. Accessed February 2014.
[5] Clinicaltrials.gov website: http://clinicaltrials.gov/ct2/show/NCT01516879. Accessed February 2014.
[6] Clinicaltrials.gov website: http://clinicaltrials.gov/ct2/show/NCT01813422. Accessed February 2014.
[7] Clinicaltrials.gov website: http://clinicaltrials.gov/ct2/show/NCT01854918. Accessed February 2014.