Anacetrapib (Merck & Co., Inc.) is a cholesteryl ester transfer protein (CETP) inhibitor that blocks the transfer of cholesterol from high-density lipoprotein to other lipoproteins. This results in an increase in high-density lipoprotein cholesterol (HDL-C) and a decrease in low-density lipoprotein cholesterol (LDL-C), which may reduce the development of atherosclerosis. Anacetrapib has not been approved for sale in Canada or the United States.

Clinical evidence to support the use of anacetrapib for dyslipidemia has been reported in two clinical trials. An eight-week phase 2b dose-ranging study in patients with primary hypercholesterolemia or mixed hyperlipidemia reported statistically significant increases in HDL-C of up to 139% and statistically significant reductions in LDL-C of up to 40% with anacetrapib compared with placebo. The DEFINE phase 3 clinical trial showed that, when used concomitantly with a statin in patients with known coronary artery disease or who were at high-risk for coronary artery disease, anacetrapib produced a 39.8% reduction in LDL-C and a 138.1% increase in HDL-C at 24 weeks compared with placebo. These lipid changes were sustained at 76 weeks.

Anacetrapib monotherapy and coadministration with atorvastatin were generally well-tolerated. Adverse effects were mostly mild to moderate, and consisted of gastrointestinal symptoms (diarrhea, constipation, dyspepsia) and myalgias. There was no evidence of effects on blood pressure, serum levels of aldosterone, serum levels of electrolytes, or an increased risk of cardiovascular events.

REVEAL is an ongoing, large-scale phase 3 trial evaluating the long-term safety and efficacy of anacetrapib with a statin for the secondary prevention of major coronary events in patients who have a history of cardiovascular disease. Results are anticipated in January 2017.

The long-term safety and efficacy of anacetrapib for the primary or secondary prevention of cardiovascular morbidity and mortality needs to be clarified to determine the impact on clinical practice.

Background

Cardiovascular disease is one of the leading causes of morbidity and mortality in Canada. In 2009, almost 30% of all deaths in Canada were the result of cardiovascular disease. The economic burden of cardiovascular disease in Canada is substantial. The total cost for the use of health care resources and lost productivity was estimated to be $20.9 billion in 2005. This figure is expected to increase to $28.3 billion in 2020. Statin therapy has been shown to decrease LDL-C by approximately 25% to 50%, with a corresponding 24% to 40% risk reduction in cardiovascular events. However, many patients remain at risk for future cardiovascular events despite optimal treatment with statins. This may be explained, in part, by a low level of HDL-C, which has been shown to be a significant predictor of cardiovascular risk. Epidemiologic data have shown that the cardiovascular benefit from higher HDL-C levels is independent of the benefit associated with lower LDL-C levels. This suggests that strategies that increase HDL-C, when added to those that lower LDL-C, may reduce cardiovascular risk more so than approaches that focus only on decreasing LDL-C. However, this has not yet been proven in an adequately powered randomized clinical trial.

The Technology

Anacetrapib (Merck & Co. Inc., Whitehouse Station, New Jersey) is an orally active cholesteryl ester transfer protein (CETP) inhibitor. CETP is a plasma protein that facilitates the transfer of cholesterol and triglycerides between various lipoprotein fractions. HDL particles play a central role in reverse cholesterol transport, a process that removes excess cholesterol from peripheral tissues and transports it to the liver for excretion. Pharmacologic inhibition of CETP blocks the transfer of cholesterol from HDL to other lipoproteins such as LDL and very low-density lipoprotein (VLDL). The result is an accumulation of cholesterol in the HDL fraction, which may reduce the development of atherosclerosis (a narrowing of arteries due to an accumulation of fatty deposits or plaques in the arterial wall).
The development of the previous investigational CETP inhibitors torcetrapib (Pfizer Inc., New York, New York) and dalcetrapib (Roche, Basel, Switzerland) was discontinued. Despite a 72% increase in HDL-C and a 25% decrease in LDL-C, development of torcetrapib was stopped in 2006 after results from a pivotal trial showed that torcetrapib was associated with an increased risk of cardiovascular events and mortality.17 These adverse events may have been the result of “off target” effects on blood pressure and serum aldosterone levels that were unrelated to CETP inhibition.18,19 Furthermore, three studies failed to show any effect of torcetrapib on atherosclerotic plaque progression.20-22 Dalcetrapib was a relatively weak CETP inhibitor that produced a 30% increase in HDL-C and did not significantly affect LDL-C.23 The development of dalcetrapib was terminated early in 2012 when a phase 3 trial in patients with coronary artery disease failed to show clinically meaningful efficacy when added to a statin for a reduction in cardiovascular events.23,24

Regulatory Status

Anacetrapib is not currently approved for sale in Canada or the United States. Regulatory status in these countries is pending results from the international phase 3 clinical development program.

Patient Group

Dyslipidemia (an abnormal level of lipids and lipoproteins in the blood) is a major risk factor for developing cardiovascular disease.2 Higher concentrations of LDL-C and lower concentrations of HDL-C increase the risk for atherosclerosis.25 Progression of atherosclerosis may lead to coronary artery disease, myocardial infarction, heart failure, peripheral artery disease, and stroke. A substantial proportion of Canadians aged 20 to 79 years are estimated to have a high level of LDL-C (36%) and a low level of HDL-C (30%).25 An LDL-C level of 5.0 mmol/L or greater is considered high for patients at low risk of cardiovascular disease.2 An LDL-C level of 3.5 mmol/L or greater is considered high for patients at intermediate or high risk of cardiovascular disease.2 A low HDL-C level is less than 1.0 mmol/L in men and less than 1.3 mmol/L in women.25

Current Practice

Guidelines from the Canadian Cardiovascular Society recommend that the initiation of treatment for dyslipidemia should be based on the risk of coronary artery disease and lipid levels.2 Cardiovascular risk is estimated using the Framingham Risk Score based on the patient’s age, sex, lipid levels, smoking status, and presence of comorbidities such as diabetes, hypertension, familial hyperlipidemia, family history of premature cardiovascular disease, and clinical evidence of atherosclerotic cardiovascular disease. Treatment is considered in all high-risk patients, even if cholesterol levels are normal. Treatment is also considered in moderate-risk or low-risk patients, depending on the levels of LDL-C, apolipoprotein B (apo B), and non-HDL-C. The guidelines recommend LDL-C reduction with statins as the primary target of therapy. The goal of treatment is an LDL-C level of 2.0 mmol/L or less, or a 50% or greater reduction in the LDL-C level. Alternate targets include a reduction in apo B or non–HDL-C levels.

The goals of treating patients with low HDL-C levels have not been established due to the absence of evidence showing an improvement in cardiovascular outcomes with therapies that increase HDL-C alone. Niacin is currently the most effective drug for increasing HDL-C, but use is limited by adverse effects including skin flushing and liver toxicity. Fibrates (e.g., gemfibrozil) have also been shown to increase HDL-C, but are associated with muscle toxicity when used with a statin. Furthermore, several clinical trials have suggested that adding extended-release niacin26,27 or fibrates28 to a statin does not decrease the risk of cardiovascular events relative to statin monotherapy.

Methods

Literature Search Strategy

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, Embase, PubMed, and The Cochrane Library (2012, Issue 12). Grey literature was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/en/resources.grey-matters). No methodological filters were applied. The search was limited to English language documents published between January 1, 2007 and December 11, 2012. Regular alerts were established to update the search until the publication of the bulletin. Conference abstracts were excluded from the search results.

Study Selection Criteria

Phase 2 and 3 studies evaluating the efficacy and safety of anacetrapib compared with placebo or pharmacologic therapies for the treatment of dyslipidemia and cardiovascular disease were considered for inclusion in

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the evidence section of this bulletin. Unpublished data, case reports, editorials, letters, and narrative literature reviews were excluded.

### The Evidence

Clinical data to support the use of anacetrapib in dyslipidemia and coronary artery disease have been reported in a phase 2b dose-ranging study and a phase 3 clinical trial. The addition of anacetrapib to statin therapy is being studied in two ongoing phase 3 trials in patients with heterozygous familial hypercholesterolemia and Japanese patients with dyslipidemia. A large-scale, phase 3 clinical trial is evaluating whether anacetrapib reduces major coronary events in patients with a history of cardiovascular disease.

Bloomfield et al. evaluated the efficacy, safety, and tolerability of anacetrapib administered as monotherapy or with atorvastatin for the treatment of dyslipidemia in a multi-centre, randomized, double-blind, placebo-controlled, dose-ranging study. Patients aged 18 to 75 years with primary hypercholesterolemia or mixed hyperlipidemia (LDL-C values ranging from 2.6 mmol/L to 4.9 mmol/L, 2.6 mmol/L to 4.1 mmol/L for moderate-risk patients, or 2.6 mmol/L to 3.4 mmol/L for diabetic patients) were eligible for inclusion. Patients were excluded if they had a history of coronary heart disease, symptomatic carotid artery disease, uncontrolled cardiac arrhythmias, uncontrolled hypertension, or uncontrolled diabetes. Following a screening and a placebo run-in period, 589 patients were randomly allocated to one of ten groups: four groups received atorvastatin 20 mg in combination with anacetrapib 10 mg, 40 mg, 150 mg, or 300 mg; one group received atorvastatin 20 mg alone; four groups received anacetrapib 10 mg, 40 mg, 150 mg, or 300 mg monotherapy; and one group received placebo alone.

The primary outcome was the percentage change from baseline in LDL-C with anacetrapib monotherapy versus placebo, and with anacetrapib coadministered with atorvastatin versus atorvastatin alone. Secondary outcomes included percentage change from baseline in HDL-C, triglycerides, apo B (a major protein component of LDL), and apo A-I (a major protein component of HDL). Additional measurements included percentage change from baseline in other biomarkers for coronary artery disease including lipoprotein (a) and C-reactive protein. The safety assessment included blood pressure measurements, serum aldosterone levels, and serum electrolyte (sodium, potassium, chloride, bicarbonate) levels.

Baseline demographic and clinical characteristics were similar across the 10 treatment groups. The mean age was 56.4 ± 9.6 years and the majority (83.7%) of participants were Caucasian. The mean baseline levels for LDL-C and apo B were 3.7 ± 0.6 mmol/L and 3.7 ± 0.6 mmol/L, respectively. The mean baseline levels for HDL-C and apo A-I were 1.3 ± 0.3 mmol/L and 4.4 ± 0.7 mmol/L, respectively. Overall, 26 (4.0%) patients had diabetes and 223 (37.9%) had hypertension. After eight weeks of treatment, all anacetrapib monotherapy doses produced statistically significant increases in HDL-C and statistically significant decreases in LDL-C compared with placebo (P < 0.001 versus placebo for all doses). While there were statistically significant and incremental lipid changes with increasing doses from 10 mg up to 150 mg, there was no difference in response between the 150 mg and 300 mg doses. Decreases in LDL-C were accompanied by significant decreases in apo B, indicating a reduction in the concentration of circulating LDL particles. Similarly, increases in HDL-C were accompanied by significant increases in the levels of apo A-I, suggesting an increase in the concentration of circulating HDL particles. The peak effects on lipids and lipoproteins were a 40% reduction in LDL-C, a 30% reduction in apo B, a 139% increase in HDL-C, and a 47% increase in apo A-I.

Coadministration of atorvastatin with anacetrapib produced significantly greater dose-dependent reductions in LDL-C compared with atorvastatin monotherapy. The dose-dependent increases in HDL-C with coadministration of atorvastatin were significantly larger than those produced by atorvastatin monotherapy but similar to the increases observed with anacetrapib monotherapy. Coadministration of atorvastatin with anacetrapib reduced LDL-C by up to 70% and increased HDL-C by up to approximately 130% compared with baseline values. All anacetrapib monotherapy and coadministration doses produced significantly greater reductions of up to 50% in lipoprotein (a) compared with placebo and atorvastatin, respectively. Anacetrapib administration did not affect the levels of triglycerides or C-reactive protein. Sustained effects on lipids were observed eight weeks following cessation of anacetrapib treatment in the groups receiving the 150 mg and 300 mg doses.

The DEFINE trial was a multi-centre, randomized, double-blind, placebo-controlled trial assessing the efficacy and safety profile of anacetrapib for the treatment of dyslipidemia in patients with known coronary artery disease or who were at high risk for coronary artery disease (ten-year Framingham Risk Score > 20%). Patients aged...
18 years to 80 years were considered for inclusion if they had an LDL-C level ranging between 1.3 mmol/L and 2.6 mmol/L, while on a statin with or without other lipid-modifying medications, an HDL-C level less than 1.6 mmol/L, and a triglyceride level of 4.5 mmol/L or less. Patients were excluded if they had severe chronic heart failure, uncontrolled hypertension, or cardiac arrhythmias; active or chronic hepatobiliary or hepatic disease or severe renal impairment; myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, unstable angina, or stroke within the previous three months; or if they were treated with warfarin or a strong CYP3A4 inhibitor or inducer.

Following a two-week screening and a placebo run-in period, 1,623 patients were randomly allocated to receive anacetrapib 100 mg or placebo once daily. All patients received concomitant statin treatment with or without other lipid-modifying agents. The primary efficacy outcomes were the percentage change from baseline in LDL-C after 24 weeks of treatment and safety assessments (including adverse events, serum electrolyte and aldosterone levels, blood pressure readings, and electrocardiography) throughout the 76-week treatment period. Secondary efficacy outcomes included the change in LDL-C from baseline to week 76 and changes in HDL-C, apo B, and apo A-I after 24 weeks and 76 weeks of treatment. A pre-specified cardiovascular composite end point (including death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina) was used to evaluate safety. As specified by the protocol, anacetrapib was discontinued for safety reasons in any patient who had an LDL-C level of less than 0.6 mmol/L at two consecutive visits.

The two groups were matched at baseline for demographic and clinical characteristics. The average age was 63 years and the majority (83.5%) of participants were Caucasian. Most participants (54.7%) had prior coronary artery disease. The majority of patients had diabetes (53.1%) and hypertension (67.8%). There was a higher rate of discontinuation in the anacetrapib group compared with placebo due to two consecutive measurements of LDL-C levels of less than 0.6 mmol/L during the treatment period (142 patients in the anacetrapib group [17.6%] versus one patient in the placebo group [0.1%]). At 24 weeks, statistically significant changes in LDL-C and HDL-C beyond that seen with placebo were reported in the anacetrapib group — a 39.8% reduction in LDL-C and a 138.1% increase in HDL-C; \( P < 0.001 \) for both (Table 1). Statistically significant changes in apo A-I and apo B levels beyond that with placebo were also reported (\( P < 0.001 \) for both).

A 36.4% reduction in lipoprotein (a) levels beyond that seen in the placebo group was reported (\( P < 0.05 \)). Anacetrapib produced statistically significant (\( P < 0.05 \)) but clinically modest changes in C-reactive protein (18.3%) and triglycerides (−5.3%). All lipid and lipoprotein changes were sustained throughout the 76-week treatment period. Although the DEFINE study was not designed to assess cardiovascular outcomes, a post hoc analysis showed a statistically significant difference in the number of coronary revascularization procedures between groups during the 76-week treatment phase (8 [1.0%] in the anacetrapib group versus 28 [3.5%] in the placebo group; \( P = 0.001 \)).

A two-year extension of the DEFINE trial is currently ongoing and will further evaluate the long-term safety and efficacy of anacetrapib in patients with known, or at high-risk for, coronary artery disease. Participants will be assigned to the same treatment arm to which they were assigned in the base study. The total duration of the extension study will be up to 116 weeks, and will include a two-year treatment period, followed by a 12-week off-drug phase. In addition, some participants will be evaluated in an extended off-drug phase, with a total duration of one year. The estimated study completion date is November 2013.

Whether the short-term effects of anacetrapib on lipid levels translate into clinically meaningful reductions in cardiovascular events and mortality is being investigated in the ongoing REVEAL trial. This randomized, multi-centre, double-blind, placebo-controlled trial will recruit patients 50 years or older with a history of cardiovascular disease (e.g., myocardial infarction, cerebrovascular atherosclerotic disease, peripheral arterial disease, or diabetes with other evidence of symptomatic coronary artery disease). All patients will receive concomitant statin treatment. Patients allocated to receive 100 mg anacetrapib will be compared with those on placebo to determine if the addition of anacetrapib reduces the risk of major coronary events (defined as coronary death, myocardial infarction, or coronary revascularization procedure). The trial is expected to enroll 30,000 participants, who will be followed for up to four years. The estimated completion date is January 2017. Anacetrapib, when added to ongoing statin therapy, is also being studied in two phase 3 trials in patients with heterozygous familial hypercholesterolemia and in Japanese patients with dyslipidemia. The primary outcome for both studies is the percentage change from baseline in LDL-C. The percentage change in HDL-C is being assessed as a secondary outcome. Each trial is expected to enroll 300 participants and results for both are anticipated in 2014.
Table 1: Summary of DEFINE Trial Results\textsuperscript{31}

| Variable\textsuperscript{a} | Baseline | Week 24 | | Week 76 | | | |
|-----------------------------|----------|---------|--------------------------|--------------------------|
|                             | Level    | Level   | Placebo-Adjusted % Change From Baseline (95% CI) | Level | Placebo-Adjusted % Change From Baseline (95% CI) |
| HDL-C (mmol/L)              |          |         |                          |                          |
| Placebo                     | 1.0      | 1.0     | 138.1 (133.9 to 142.4)\textsuperscript{b} | 1.2 | 138.8 (134.5 to 143.0)\textsuperscript{b} |
| (n = 797)                   | (n = 744) |         |                          | (n = 664)                |
| Anacetrapib                 | 1.0      | 2.6     |                          | 2.6 |                          |
| (n = 797)                   | (n = 686) |         |                          | (n = 541)                |
| LDL-C (mmol/L)              |          |         |                          |                          |
| Placebo                     | 2.1      | 2.0     | −39.8 (−42.1 to −37.5)\textsuperscript{b} | 2.0 | −36.2 (−38.7 to −33.6)\textsuperscript{b} |
| (n = 794)                   | (n = 742) |         |                          | (n = 663)                |
| Anacetrapib                 | 2.1      | 1.2     |                          | 1.3 |                          |
| (n = 794)                   | (n = 683) |         |                          | (n = 536)                |
| Apo A-I (g/L)               |          |         |                          |                          |
| Placebo                     | 1.4      | 1.4     | 44.7 (42.8 to 46.5)\textsuperscript{b} | 1.4 | 42.3 (40.5 to 44.1)\textsuperscript{b} |
| (n = 780)                   | (n = 777) |         |                          | (n = 675)                |
| Anacetrapib                 | 1.4      | 2.1     |                          | 2.0 |                          |
| (n = 778)                   | (n = 774) |         |                          | (n = 571)                |
| Apo B (g/L)                 |          |         |                          |                          |
| Placebo                     | 0.9      | 0.9     | −21.0 (−22.7 to −19.3)\textsuperscript{b} | 0.9 | −18.3 (−20.2 to −16.4)\textsuperscript{b} |
| (n = 779)                   | (n = 777) |         |                          | (n = 675)                |
| Anacetrapib                 | 0.9      | 0.7     |                          | 0.7 |                          |
| (n = 780)                   | (n = 775) |         |                          | (n = 572)                |
| Triglycerides (mmol/L)      |          |         |                          |                          |
| Placebo                     | 1.4      | 1.4     | −6.8 (−9.9 to −3.9)\textsuperscript{c} | 1.4 | −5.3 (−8.9 to −1.7)\textsuperscript{c} |
| (n = 797)                   | (n = 744) |         |                          | (n = 667)                |
| Anacetrapib                 | 1.4      | 1.3     |                          | 1.2 |                          |
| (n = 799)                   | (n = 689) |         |                          | (n = 544)                |
| Lipoprotein (a) (nmol/L)    |          |         |                          |                          |
| Placebo                     | 25.9     | 29.6    | −36.4 (−40.7 to −32.3)\textsuperscript{c} | 31.3 | −38.8 (−44.5 to −33.9)\textsuperscript{c} |
| (n = 768)                   | (n = 765) |         |                          | (n = 668)                |
| Anacetrapib                 | 26.8     | 14.8    |                          | 16.4 |                          |
| (n = 762)                   | (n = 758) |         |                          | (n = 560)                |
| C-reactive protein (mmol/L) |          |         |                          |                          |
| Placebo                     | 15.2     | 15.2    | 10.0 (3.2 to 16.7)\textsuperscript{c} | 13.3 | 18.3 (10.7 to 25.5)\textsuperscript{c} |
| (n = 783)                   | (n = 776) |         |                          | (n = 681)                |
| Anacetrapib                 | 13.3     | 16.2    |                          | 14.3 |                          |
| (n = 779)                   | (n = 776) |         |                          | (n = 573)                |

Apo = apolipoprotein; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

\textsuperscript{a}Levels and placebo-adjusted percentage changes from baseline (changes from baseline beyond that with placebo) are means for all variables, except for triglycerides, lipoprotein (a), and C-reactive protein for which medians are shown.

\textsuperscript{b}P < 0.001.

\textsuperscript{c}P < 0.05.
Adverse Effects

Anacetrapib monotherapy and coadministration with atorvastatin were generally well-tolerated. Safety assessments from the two completed trials show no evidence that anacetrapib has an effect on blood pressure, serum aldosterone levels, or serum electrolyte levels.29,31 The overall incidence of adverse events of anacetrapib in the dose-ranging study was similar to placebo, and no dose-related trends were identified.29 Constipation, diarrhea, dyspepsia, and myalgia were the most prevalent adverse events attributed to treatment, and no patient experienced or discontinued therapy due to serious adverse events.29 Some non–dose-related incidences of clinically relevant elevations in liver enzymes and creatine kinase were reported. However, there were no cases of hepatitis, myopathy, or rhabdomyolysis.29 During the DEFINE trial, no significant differences were noted between the anacetrapib and placebo group in the percentage of patients experiencing adverse effects that were thought to be related to the study drug or that led to its discontinuation.31 There were no significant differences between the two groups in the mean change in systolic or diastolic blood pressure or in the percentage of patients reporting an increase in blood pressure. There were no significant differences in the percentages of patients with myalgias or elevations in creatine kinase. There were no cases of rhabdomyolysis in either study group. Fewer patients in the anacetrapib group compared with the placebo group had liver enzymes greater than three times the upper reference limit (0.1% versus 1%; \( P = 0.02 \)). Death from any cause occurred in 11 (1.4%) patients in the anacetrapib group and 8 (1.0%) patients in the placebo group (\( P = 0.50 \)). A minority of these deaths were due to cardiovascular causes (4 [36.4%] in the anacetrapib group and 1 [12.5%] in the placebo group). The pre-specified adjudicated cardiovascular composite end point (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina) occurred in 16 (2.0%) patients treated with anacetrapib compared with 21 (2.6%) patients receiving placebo (\( P = 0.40 \)). Additional analyses suggested that anacetrapib would not be associated with an increase in cardiovascular events as previously seen with torcetrapib.31

Cost

The manufacturer’s price for anacetrapib is currently unavailable, as it has not been approved for sale in Canada.

Concurrent Developments

Evacetrapib (Eli Lilly and Co., Indianapolis, Indiana) is another CETP inhibitor currently under investigation. A 12-week phase 2 trial in 398 patients with dyslipidemia showed that evacetrapib administered as monotherapy produced statistically significant increases in HDL-C of up to 128.8% and statistically significant decreases in LDL-C of up to 35.9% (\( P < 0.001 \) compared with placebo).36 A statistically significant reduction in the level of triglycerides was also observed with the administration of the highest dose of evacetrapib (10.8%; \( P = 0.006 \) compared with placebo). Compared with evacetrapib monotherapy, the combination of a statin and evacetrapib resulted in greater reductions in LDL-C but no greater increase in HDL-C. Evacetrapib had no effect on blood pressure or serum aldosterone levels. A phase 3 trial is currently evaluating the efficacy of evacetrapib for the prevention of cardiovascular events in patients with high-risk cardiovascular disease (those with a history of acute coronary syndrome, cerebrovascular atherosclerotic disease, peripheral arterial disease, or diabetes with documented coronary artery disease).37 The primary outcome measure will be time to first occurrence of the composite end point of cardiovascular death, myocardial infarction, stroke, coronary revascularization procedure, or hospitalization for unstable angina. An estimated 11,000 participants will be enrolled and followed for an estimated four years. The expected completion date is September 2015.

Another CETP inhibitor (DEZ-001, Dezima Pharma, Amsterdam, the Netherlands) is set to begin phase 3 testing.38 Three other CETP inhibitors — BAY 60-5521 (Bayer, Leverkusen, Germany),39 JTT-302 (Japan Tobacco Inc., Tokyo, Japan),40 and DRL-17822 (Dr. Reddy’s Laboratories Limited, Andhra Pradesh, India)41 — have all undergone phase 2 testing but do not currently have any ongoing trials.

Other HDL-C-raising treatment strategies currently under phase 2 investigation include reconstituted forms of HDL or apo A-I mimetics (the use of short peptides to mimic the function of native apo A-I and potentially enhance the functions of HDL), apo A-I-based infusion therapies that may also enhance HDL functionality, and
RVX-208 (the first orally available compound that induces apo A-I transcription in hepatocytes). The Lipid Sciences Plasma Delipidation System-2 (Lipid Sciences Inc, Pleasanton, California) is an investigational device that selectively removes cholesterol from HDL in samples of human plasma collected by apheresis. A feasibility study has shown that autologous delipidated HDL plasma infusions were well-tolerated and resulted in a non-significant trend toward atherosclerotic plaque regression. Monoclonal antibodies targeted against proprotein convertase subtilisin/kexin type 9 (PCSK9) to reduce LDL-C are also in development.

Two PCSK9 inhibitors, REGN727/SAR236553 (Sanofi New York, New York/Regeneron Pharmaceuticals Inc., Tarrytown, New York) and AMG 145 (Amgen Inc., Thousand Oaks, California) are currently entering phase 3 trials. Other investigational lipid-lowering therapies in phase 2 and 3 trials include lomitapide (a microsomal transfer protein inhibitor that decreases triglycerides and VLDL), mipomersen (an mRNA inhibitor of apo B that lowers LDL), and GFT505 (a peroxisome proliferator activator that decreases triglycerides and increases HDL).

Rate of Technology Diffusion

The DEFINE trial was primarily designed to determine if the “off target” adverse effects on blood pressure and serum aldosterone levels observed with torcetrapib would also occur with anacetrapib. It lacked the sample size and study duration to assess the long-term safety and efficacy of anacetrapib for the improvement of cardiovascular outcomes. Results from the larger population in the REVEAL trial will help determine whether lipid modification with anacetrapib, in addition to statin therapy, is effective for the secondary prevention of major coronary events in patients who have a history of cardiovascular disease. The diverse ethnic population and broad inclusion criteria for participation, combined with the large number of participants, will not only help evaluate the primary hypothesis that CETP inhibition reduces cardiovascular risk but will also facilitate subgroup analyses to determine if there are categories of patients who may benefit more from therapy with anacetrapib.

Implementation Issues

Anacetrapib has been shown to significantly increase HDL-C by over 130% and decrease LDL-C by 40% in patients with dyslipidemia and coronary artery disease. Anacetrapib does not appear to affect serum levels of aldosterone or electrolytes, or increase blood pressure. Although these results are promising, there is considerable controversy regarding the use of HDL-C as a therapeutic target. It is not yet clear whether the HDL particles generated by inhibition of CETP retain their protective function against atherosclerosis. While investigators have reported that pharmacologic CETP inhibition does not impair the lipid-mobilizing activities of HDL, the effect on other antiatherosclerotic properties (including antithrombotic, antiinflammatory, antioxidative, antiplatelet, and vasodilatory functions) has not been extensively investigated. Current clinical assays that simply measure the total cholesterol content in HDL particles cannot assess qualitative functional differences in these activities. More research is needed to address not only HDL quantity but also the functional quality of the resulting HDL particles.

Whether the lipid modifications seen with anacetrapib translate into a clinically meaningful reduction in the risk of cardiovascular events remains an important question. A reduction in cardiovascular risk has not been consistently observed among patients with genetically reduced CETP function. Furthermore, the effect of increasing HDL-C on the residual cardiovascular risk after statin therapy remains uncertain. No trial to date has shown that HDL-C-increasing therapies result in an additional cardiovascular risk reduction when added to statin therapy. It is possible that any benefit of anacetrapib on cardiovascular outcomes may be due to incremental lowering of LDL-C beyond that achieved with statins. Furthermore, there is some evidence to suggest that, in the setting of primary prevention of cardiovascular disease and in the presence of very low concentrations of LDL-C, HDL-C concentration might not predict cardiovascular risk. To ensure appropriate patient selection for anacetrapib therapy, further research is needed to determine if certain subgroups respond better to anacetrapib with or without concomitant statin therapy.

If adopted into clinical practice, anacetrapib may be considered an adjunctive therapy to statins and other treatments for dyslipidemia. Until the results of the REVEAL trial are reported and the effects on cardiovascular outcomes are made available, the potential cost consequences of introducing anacetrapib as a therapeutic option for dyslipidemia are unknown but may likely add to the overall cost of treatment. In summary, the long-term safety and efficacy of anacetrapib for the primary or secondary prevention of
cardiovascular morbidity and mortality needs to be clarified to determine the potential impact of this agent in the clinical management of dyslipidemia.

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