

# HDL Soared, LDL Dropped With Anacetrapib

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FROM THE ANNUAL SCIENTIFIC SESSIONS  
OF THE AMERICAN HEART ASSOCIATION

CHICAGO – The experimental oral agent anacetrapib increased HDL cholesterol levels by a staggering 138%, compared with placebo, in high-risk patients and did so without the negative side effects that plagued another drug in the same class.

When compared with placebo at 24 weeks, once-daily anacetrapib increased HDL levels from 40 mg/dL to 101 mg/dL and decreased LDL levels by 40%

from 81 mg/dL to 45 mg/dL in the double-blind phase III Determining the Efficacy and Tolerability of CETP Inhibition With Anacetrapib (DEFINE) trial.

“This is a total change in what lipids can be,” said senior investigator Dr. Christopher Cannon, who went one step further in a statement describing anacetrapib as having a “knock-your-socks-off effect on HDL and a jaw-dropping effect on LDL” among 1,623 patients already taking a cholesterol-lowering statin and had LDL levels consistent with recommended guidelines.

Anacetrapib is a cholesteryl ester transfer protein (CETP) inhibitor designed to fight hypercholesterolemia by raising levels of HDL. The strategy was called into question, however, after the experimental CETP inhibitor torcetrapib was found to have off-target effects in the adrenal glands, leading to increased blood pressure, mortality, and cardiovascular events.

Anacetrapib had an acceptable side-effect profile, with no effects on blood pressure electrolytes or aldosterone through 76 weeks of follow-

up, Dr. Cannon, with Brigham and Women’s Hospital, Boston, reported at a press briefing at the meeting. The pre-specified, adjudicated composite end point of death from cardiovascular causes, MI, hospitalization for unstable angina,



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na, or stroke occurred in 16 anacetrapib-treated patients and in 21 placebo-treated patients.

Although the trial was not designed as an outcome study, a Bayesian analysis indicated a 94% predictive probability that anacetrapib would not increase cardiovascular events by 25% as seen with torcetrapib.

In addition, anacetrapib reduced the need for revascularization by two-thirds, compared with placebo (8 patients vs. 28 patients), a finding that Dr. Cannon said convinced him that the strategy of CETP inhibition works.

The REVEAL follow-up trial of anacetrapib vs. placebo is being launched in Europe, North America, and Asia in 30,000 patients with occlusive arterial disease, with a primary end point of coronary death, MI, or coronary revascularization, Dr. Cannon announced during the press conference.

Reporters questioned whether increasing HDL really matters, to which Dr. Jessup remarked that HDL is a potent marker of risk and that older data showed that niacin, which also works by increasing HDL, decreased the need for revascularization. Two trials of niacin are also underway that may provide more contemporary data.

There is some concern that the drug might be too powerful and potentially push levels too low, as 18% of patients had to discontinue treatment after their LDL cholesterol level fell below 25 mg/dL.

Follow-up from REVEAL is planned in 4 years, which means that barring any new safety signals, anacetrapib would be submitted for approval in about 2015, Dr. Cannon said in an interview.

Results of DEFINE were published online simultaneously with Dr. Cannon’s presentation (N. Engl. J. Med. 2010 [doi:10.1056/NEJMoa1009744]). ■

## VITALS

**Major Finding:** At 24 weeks, once-daily anacetrapib increased HDL cholesterol levels from 40 mg/dL to 101 mg/dL and decreased LDL levels from 81 mg/dL to 45 mg/dL, both highly significant differences from placebo.

**Data Source:** DEFINE, a phase III trial in 1,623 patients with or at high risk for coronary heart disease.

**Disclosures:** DEFINE was supported by Merck Research Laboratories. Dr. Cannon and his coauthors report financial relationships with several pharmaceutical firms including Merck. Dr. Cannon also serves as an adviser and holds equity in Automedics Medical Systems.

observed in an additional 22 patients 12 to 17 years of age who were treated with DULERA in another clinical trial. The safety and efficacy of DULERA have not been established in children less than 12 years of age.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm per year (range 0.3 to 1.8 per year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

The growth of children and adolescents receiving orally inhaled corticosteroids, including DULERA, should be monitored routinely (e.g., via stadiometry). If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including DULERA, each patient should be titrated to his/her lowest effective dose [see *Dosage and Administration* (2.2)].

### 8.5 Geriatric Use

A total of 77 patients 65 years of age and older (of which 11 were 75 years and older) have been treated with DULERA in 3 clinical trials up to 52 weeks in duration. Similar efficacy and safety results were observed in an additional 28 patients 65 years of age and older who were treated with DULERA in another clinical trial. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other products containing beta<sub>2</sub>-agonists, special caution should be observed when using DULERA in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta<sub>2</sub>-agonists. Based on available data for DULERA or its active components, no adjustment of dosage of DULERA in geriatric patients is warranted.

### 8.6 Hepatic Impairment

Concentrations of mometasone furoate appear to increase with severity of hepatic impairment [see *Clinical Pharmacology* (12.3)].

## 10 OVERDOSAGE

### 10.1 Signs and Symptoms

**DULERA:** DULERA contains both mometasone furoate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to DULERA.

**Mometasone Furoate:** Chronic overdosage may result in signs/symptoms of hypercorticism [see *Warnings and Precautions* (5.7)]. Single oral doses up to 8000 mcg of mometasone furoate have been studied on human volunteers with no adverse reactions reported.

**Formoterol Fumarate:** The expected signs and symptoms with overdosage of formoterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the following signs and symptoms: angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. Cardiac arrest and even death may be associated with an overdose of formoterol.

The minimum acute lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 63,000 times the MRHD on a mcg/m<sup>2</sup> basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the MRHD.

### 10.2 Treatment

**DULERA:** Treatment of overdosage consists of discontinuation of DULERA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of DULERA. Cardiac monitoring is recommended in cases of overdosage.

Manufactured by 3M Health Care Ltd.,  
Loughborough, United Kingdom.  
Manufactured for Schering Corporation, a subsidiary of



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