

For release to UK consumer media

## **Landmark ‘IMPROVE-IT’ Trial Results: Ezetimibe/Simvastatin Combination Significantly Reduces More Cardiovascular Events Than Simvastatin Alone in Patients Presenting with Acute Coronary Syndromes**

*One of the longest and largest global cardiovascular outcomes trial in over 18,000 patients with Acute Coronary Syndromes demonstrates that reaching lower cholesterol levels with the cholesterol inhibitor ezetimibe, in combination with a statin, reduces cardiovascular events in high-risk acute coronary syndrome patients*

**Hoddesdon, Nov. 18, 2014** – MSD has announced that the investigational IMPROVE-IT study has met its primary and all secondary composite efficacy endpoints.<sup>1</sup> Treatment with ezetimibe/simvastatin (simvastatin in combination with ezetimibe) significantly reduced cardiovascular events more than simvastatin alone in patients presenting with Acute Coronary Syndromes (ACS), even though the enrolled patients’ LDL-cholesterol, ‘bad cholesterol’, levels were already around current recommended targets.<sup>1</sup> The results from this 18,144-patient study of high-risk patients presenting with ACS, which began in 2005, have been presented during the late-breaking clinical trials session at the American Heart Association 2014 Scientific Sessions.<sup>1</sup>

Cardiovascular disease (term for all diseases affecting the heart and circulatory system) is the UK’s biggest killer and despite the decline in death rates in recent years, it caused 180,000 deaths in

ACS is an umbrella term for a heart attack or episode of unstable angina. In the UK, almost a third of patients who have had a heart attack will go on to have a subsequent cardiovascular event in the first year.<sup>3</sup> The IMPROVE-IT trial was the first to investigate whether the ‘lower is better’ relationship (that lower cholesterol levels are associated with a reduced risk of cardiovascular events<sup>4</sup>) is maintained at cholesterol levels below current targets, in high risk ACS patients, when adding a non-statin cholesterol absorption inhibitor to a statin.<sup>1,5</sup>

### **Study results:**

- Patients taking the LDL-cholesterol lowering medicine ezetimibe/simvastatin experienced significantly fewer major cardiovascular events than patients treated with simvastatin alone (as measured by a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, re-hospitalisation for unstable angina or coronary revascularisation occurring at least 30 days after randomisation).<sup>1</sup>

- At seven years, 32.7 per cent of patients taking ezetimibe/simvastatin experienced a primary endpoint event compared to 34.7 per cent of patients taking simvastatin alone (hazard ratio of 0.936, p=0.016).<sup>1</sup>
- Based on the LDL-cholesterol range compared in the study's treatment arms (at one year, a mean LDL-C of 53 mg/dL (1.37mmol/L) versus 70 mg/dL (1.81 mmol/L), respectively for ezetimibe/simvastatin, and simvastatin alone)<sup>1</sup> the 6.4 per cent relative risk reduction observed in the ezetimibe/simvastatin arm<sup>1</sup> in this clinical trial was consistent with the treatment effect that had been projected based on prior studies of statins.<sup>4,5</sup>

There were 33 IMPROVE-IT UK clinical trial sites. Dr Mark Signy, Consultant Cardiologist UK IMPROVE-IT investigator, comments, "The results today from IMPROVE-IT provide a real step-forward in our understanding of the role of LDL-cholesterol reduction in preventing cardiovascular disease. We have known for many years that reducing LDL-cholesterol with statins has a major benefit in reducing cardiovascular disease. We also know that ezetimibe can further significantly reduce LDL-cholesterol when used in combination with a statin. What we have now is outcome data to show that LDL-cholesterol reduction with a combination of ezetimibe/simvastatin, in comparison with a statin alone, has a significant and well-tolerated further cardiovascular benefit in high risk patients, even those with relatively low baseline cholesterol levels; this is a very welcome further missing piece of a very complex puzzle."

Current guidelines such as the European Society Guidelines<sup>6</sup> and Joint British Society Guidelines<sup>7</sup> recommend an LDL-C target of 1.8mmol/L (or equivalent), based on available evidence from statin trials to date.<sup>4</sup> IMPROVE-IT aimed to reduce patients' cholesterol levels to a normal range seen in an ancestral human 'hunter-gatherer' or healthy human newborn (first 28 days), that is between approximately 1.3mmol/L to 1.8mmol/L.<sup>8</sup> IMPROVE-IT posed the question 'would lowering LDL-C even further by adding a non-statin cholesterol absorption inhibitor to a statin protect people from cardiovascular events?'<sup>1</sup>

Dr. Mike Kirby, GP, Hertfordshire, comments, "There is a widening gap between our ancient genetically determined biology and the nutritional, cultural and activity patterns of modern life, which has led to the emergence of diseases such as cardiovascular disease. IMPROVE-IT confirms that by combining a non-statin agent, ezetimibe, with a statin to achieve levels of LDL-cholesterol in line with our ancestors, or a healthy newborn, we can lower some of the remaining risk of cardiovascular events in people at very high risk of a heart attack or stroke. This landmark

trial reinforces the well-documented 'lower is better' relationship between bad cholesterol levels and reduction in cardiovascular events, even at very low baseline levels of cholesterol.”

There were no significant differences between treatment groups in adverse events of special interest, which included myopathy and rhabdomyolysis, gallbladder adverse events, liver enzyme elevations greater than or equal to three times the upper limit of normal (ULN) and cancer.<sup>1</sup> These safety findings from the IMPROVE-IT study were generally consistent with the current UK Summary of Product characteristics and Patient Information Leaflet for ezetimibe (Ezetrol).<sup>9,10</sup> Among 9,067 patients in the ezetimibe/simvastatin group vs. 9,077 patients in the simvastatin group, myopathy was reported in 0.2 percent vs. 0.1 percent of patients, respectively; rhabdomyolysis was reported in 0.1 percent vs. 0.2 percent; gallbladder-related adverse events were reported in 3.1 percent vs. 3.5 percent; cholecystectomy was reported in 1.5 percent vs. 1.5 percent; and alanine aminotransferase (ALT) and/or aspartate transaminase (AST) elevations (greater than or equal to three times ULN, consecutive) were reported in 2.5 percent vs. 2.3 percent of patients.<sup>1</sup> Over seven years, cancer was reported in 10.2 percent of patients in both treatment groups.<sup>1</sup>

Ezetimibe is not currently licensed to reduce cardiovascular events. MSD plans to submit the data from IMPROVE-IT to the European Medicines Agency in mid-2015 to support a new indication for reduction of major cardiovascular events for ezetimibe, and ezetimibe in combination with simvastatin. Further information on current European licensed indications for both medicines are provided in the notes to editors.<sup>9,11</sup>

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### **Additional information about the IMPROVE-IT study**

IMPROVE-IT (IMPROved Reduction of Outcomes: VYTORIN Efficacy International Trial), was an international, multi-center, randomised, double-blind active comparator trial of 18,144 high-risk patients presenting with acute coronary syndromes (ACS), including unstable angina (UA), non-ST-segment elevation acute myocardial infarction (NSTEMI), and ST-segment elevation acute myocardial infarction (STEMI). The study assessed the incidence of major cardiovascular events, as measured by a composite of cardiovascular death, non-fatal MI, non-fatal stroke, re-hospitalisation for ACS, or coronary revascularisation (occurring 30 days or more after the initial event), in patients treated with ezetimibe/simvastatin compared with patients treated with simvastatin alone.<sup>1,12,13</sup>

All patients in the trial were started at doses of ezetimibe/simvastatin 10/40 mg or simvastatin 40 mg. Prior to a 2011 protocol amendment, the dose could be titrated to ezetimibe/simvastatin 10/80 mg or simvastatin 80 mg if successive LDL-C values exceeded 79 mg/dL (2 mmol/L).<sup>12</sup> The study enrolled patients within 10 days of ACS hospitalisation who had sufficient risk as defined in the protocol and who had an initial LDL-C of  $\leq 125$  mg/dL (3.2 mmol/L) if lipid-lowering drug naïve or  $< 100$  mg/dL (2.6 mmol/L) if on a prior prescription lipid-lowering therapy identified as no more potent than simvastatin 40 mg/day.<sup>1,12,13</sup>

### **IMPROVE-IT compared very low LDL-C levels -- a range at or below 70 mg/dL (1.81 mmol/L).<sup>1</sup>**

The LDL-C entry limitations were designed to enroll patients reasonably anticipated to achieve LDL-C levels of 70 mg/dL (1.81 mmol/L)<sup>13,14</sup> or less in the simvastatin only cohort, which was the optional recommended target set in the 2004 update to the Adult Treatment Panel (ATP) III guidelines.<sup>15</sup> This is also in line with the The European Society of Cardiology guidelines that recommend  $< 1.8$  mmol/L for those at very high risk or a 50% LDL cholesterol reduction when the target level cannot be reached.<sup>6</sup>

At one year, the mean LDL-C level was 1.37 mmol/L (53 mg/dL) in the ezetimibe/simvastatin and 1.81 mmol/L (70 mg/dL) in the simvastatin group, with a between-group difference of 0.44 mmol/L (17 mg/dL).<sup>1</sup> Prior cardiovascular outcomes studies of statins have not compared treatments at such low LDL-C levels (see Table).<sup>13</sup> At the start of the study, the average baseline LDL-C was approximately 95 mg/dL (2.46 mmol/L).<sup>1</sup> Among treatment-naïve patients (about two-thirds of those in the study), the mean baseline LDL-C was 101 mg/dL (2.62 mmol/L).<sup>1</sup> Among patients on prior lipid lowering therapy at enrollment, the mean baseline LDL-C was 80 mg/dL (2.07 mmol/L).<sup>1</sup>

<b>Table: LDL-C Comparison Ranges Between Treatment Arms in Selected Trials<sup>13</sup></b>					
<b>Trial</b>	<b>IDEAL (2005)</b>	<b>TNT (2005)</b>	<b>PROVE-IT (2004)</b>	<b>A to Z (2004)</b>	<b>IMPROVE-IT (2014)</b>
<b>LDL-C Comparison Range (mg/dL)<sup>§</sup></b>	104 vs. 81	100 vs. 77	95 vs. 62	77 vs. 63	70 vs. 53
<sup>§</sup> All values are expressed as means except PROVE-IT and A to Z, which are expressed as medians.					

### **Additional efficacy and safety results from IMPROVE-IT<sup>1</sup>**

Patients in IMPROVE-IT were initially randomised to treatment with ezetimibe/simvastatin 10/40 mg or simvastatin 40 mg. Patients were followed for up to nine years, with a median clinical follow-up of approximately six years. In this event-driven study, 5,314 primary endpoint events were reported. In addition to the significant result on the primary composite efficacy endpoint, patients taking ezetimibe/simvastatin experienced significant reductions compared to patients taking simvastatin alone on the three secondary composite efficacy endpoints, as follows:

- Ezetimibe/simvastatin reduced the incidence of the composite endpoint of death due to all causes, major coronary events, and non-fatal stroke; this endpoint occurred in 38.7 percent of patients taking ezetimibe/simvastatin and 40.3 percent of patients taking simvastatin only (hazard ratio of 0.948, p=0.034).
- Ezetimibe/simvastatin reduced the incidence of the composite endpoint of death due to coronary heart disease (CHD), non-fatal myocardial infarction (MI), and urgent coronary revascularisation with either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) occurring at least 30 days after randomisation; this endpoint occurred in 17.5 percent of patients taking ezetimibe/simvastatin and 18.9 percent of patients taking simvastatin only (hazard ratio of 0.912, p=0.016).
- Ezetimibe/simvastatin reduced the incidence of the composite endpoint of cardiovascular death, non-fatal MI, documented unstable angina that requires admission into a hospital, all revascularisation (including both coronary and non-coronary) occurring at least 30 days after randomisation, and non-fatal stroke; this endpoint occurred in 34.5 percent of patients taking ezetimibe/simvastatin and 36.2 percent of patients taking simvastatin only (hazard ratio of 0.945, p=0.035).

For additional information about the study, a backgrounder on the IMPROVE-IT trial and an IMPROVE-IT timeline are available.

## About Ezetimibe

- Ezetimibe is a cholesterol absorption inhibitor, licensed for the following indications<sup>9</sup>:
  - Ezetimibe, co-administered with a statin, is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone
  - Ezetimibe monotherapy is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated
  - Ezetimibe, co-administered with a statin, is indicated as adjunctive therapy to diet in patients with Homozygous Familial Hypercholesterolaemia. Patients may also receive adjunctive treatments
  - Ezetimibe is indicated as adjunctive therapy to diet in patients with homozygous familial sitosterolaemia
- With simvastatin as a combination product, ezetimibe is licensed for the following indications<sup>11</sup>:
  - As adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate
  - In a combination product with simvastatin, ezetimibe is indicated as adjunctive therapy for diet for use in patients with Homozygous Familial Hypercholesterolaemia. Patients may also receive adjunctive treatments (e.g. low-density lipoprotein apheresis)
- In clinical studies, the overall incidence of side effects was similar between ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between ezetimibe and placebo.<sup>9</sup>
  - The most common side effects ( $\geq 1/100$  to  $< 1/10$ ) include abdominal pain; diarrhoea; flatulence and feeling tired.<sup>10</sup>
  - Less frequent side effects (up to 1%) include increases in liver transaminases, elevation of muscle (CK) function, cough, indigestion, heartburn, nausea, joint pain, muscle spasms, decreased appetite, pain, hot flushes, chest pain, or high blood pressure.<sup>10</sup>
- Adding ezetimibe to statin therapy has been found to have a similar side effect profile to using statin therapy alone.<sup>9</sup>
- For more information an additional ezetimibe backgrounder is available and the ezetimibe SmPC can be found at: <http://www.medicines.org.uk/emc/medicine/12091><sup>9</sup>
- The SmPC for the combination therapy (ezetimibe/simvastatin) can be found at: <http://www.medicines.org.uk/emc/medicine/15657><sup>11</sup>

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Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; MSD’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of MSD’s patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

MSD undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in MSD’s 2013 Annual Report on Form 10-K and the company’s other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site ([www.sec.gov](http://www.sec.gov)).

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