News Release

Landmark trial results demonstrate significant reduction in cardiovascular events among high risk patients presenting with acute coronary syndromes when treated with ezetimibe/simvastatin combination when compared to treatment with simvastatin alone

Dublin, November 2014: The results of one of the largest and longest running global trials investigating cholesterol and cardiovascular disease (CVD) proves that lowering levels of low density lipoprotein (LDL) cholesterol with a unique combination of two drugs – simvastatin and ezetimibe – can significantly reduce events such as heart attack or stroke in high risk patients when compared to simvastatin use alone[1]. The results were announced by global healthcare company MSD following a presentation at the American Heart Association 2014 Scientific Sessions.

The IMPROVE-IT study of 18,144 patients presenting with acute coronary syndromes, was designed by the TIMI Study group and run by some of the world's leading cardiologists. The study demonstrated a 6.4 percent relative risk reduction in of cardiovascular events (including heart attacks and strokes) on top of the substantial reduction in CV risk already provided by simvastatin alone. It also found that after seven years, 32.7% of patients taking the simvastatin/ezetimibe drug combination experienced a CV event such as a heart attack or stroke, compared to 34.7% of those treated with simvastatin alone.

Cardiovascular disease – the term used to categorise all diseases affecting the heart and circulatory system such as heart attack and stroke – is the primary cause of death in Ireland and according to the Irish Heart Foundation and accounts for 33% of all deaths[2].

Statins (e.g. simvastatin) are the most commonly prescribed drugs for lowering LDL cholesterol[3] and work by reducing its production by the body[4]. Ezetimibe meanwhile works by preventing LDL cholesterol from being absorbed by the gut[5].

Statins are highly effective at reducing LDL cholesterol[6] but nonetheless high-risk patients continue to be at risk of CV events, such as heart attack or stroke. Therefore the study was

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developed to address whether lowering LDL cholesterol even further by adding ezetimibe to simvastatin further reduced these events.

The IMPROVE-IT trial is the first clinical trial to demonstrate incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy alone. It answers the question whether 'even lower is even better' when it comes to LDL cholesterol and reaffirms the LDL cholesterol hypothesis that lowering LDL cholesterol prevents cardiovascular events[7].

Speaking from the AHA Scientific Session Professor Ian Graham, Professor of Cardiovascular Medicine in Trinity College Dublin said: "The IMPROVE-IT trial confirms that, in subjects with coronary heart disease, the lower the LDL cholesterol the better. It also demonstrates that for patients who either cannot tolerate a high-intensity statin or cannot control their LDL levels through statin use alone, there is now potentially another treatment option. This trial will therefore have an impact on the management of Irish patients with vascular disease going forward."

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 and additional efficacy and safety results from the IMPROVE-IT trial are provided in the notes to editors below.

-ENDS-

NOTES TO EDITORS

Efficacy and Safety Results from IMPROVE-IT

Patients taking the LDL-cholesterol lowering medicine ezetimibe/simvastatin experienced significantly fewer major cardiovascular events than patients treated with simvastatin alone. This was 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.

Patients in IMPROVE-IT were initially randomized to treatment with ezetimibe 10mg / simvastatin 40mg or simvastatin 40mg. 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 combination 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 revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) occurring at least 30 days after randomization; 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 revascularization (including both coronary and non-coronary) occurring at least 30 days after randomization, 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).

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. These safety findings from IMPROVE-IT were generally consistent with current labeling for ezetimibe. 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. Over seven years, cancer was reported in 10.2 percent of patients in both treatment groups.

About ezetimibe/simvastatin & ezetimibe

For full safety and prescribing information see**:**

Ezetimibe/simvastatin -

http://www.medicines.ie/searchresults.aspx?term=INEGY&searchtype=AdvancedSearch

Ezetimibe -

http://www.medicines.ie/searchresults.aspx?term=Ezetrol&searchtype=AdvancedSearch

About MSD in Ireland

Known as MSD worldwide, and as Merck in the United States and Canada, MSD has operations in more than 140 countries. In Ireland, MSD employs over 2,000 people across its five sites in Dublin, Carlow, Cork, Tipperary and Wicklow. Its extensive Irish operations encompass manufacturing, commercial and marketing facilities.

MSD is a leader in healthcare, dedicated to helping the world be well through a wide range of innovative health solutions. This includes the development, production and distribution of prescription medicines, vaccines and biologic therapies as well as animal health products.

MSD's commitment to research and to increasing access to healthcare across the world is demonstrated by clearly focused policies, far-reaching programmes and life-enhancing partnerships.

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[1] Cannon C.P., IMPROVE-IT Trial: A Comparison of Ezetimibe/Simvastatin vs Simvastatin Monotherapy on Cardiovascular Outcomes After Acute Coronary Syndromes. Late Breaking Session Presented at AHA 2014; 17 November 2014.

[2] Irish Heart Foundation - http://www.irishheart.ie/iopen24/facts-heart-disease-stroke-t-7_18.html

[3] HSE: Primary Care Reimbursement Service Statistical Analysis of Claims & Payments 2012 - http://www.hse.ie/eng/staff/PCRS/PCRS_Publications/PCRSannreport12.pdf

[4] HSE: cholesterol-lowering medicines, statins - http://www.hse.ie/portal/eng/health/az/S/Statins/

[5] Medicines.ie: EZETROL summary of product characteristics - http://www.medicines.ie/medicine/7448/SPC/EZETROL+10+mg+Tablets/

[6] Vaughan C. & O'Sullivan. J. Statin Therapy in the Management of Dyslipidaemia - http://www.irishheart.ie/media/pub/heartwise/2006/statindyslipidaemia.pdf

[7] IMPROVE-IT TIMI 40 - http://www.timi.org/index.php?page=improve-it-timi-40