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Press Release

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Independent analyses of the SEAS, SHARP and IMPROVE-IT studies of ezetimibe

The University of Oxford Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) proposed that the hypothesis-generating results of the SEAS trial of ezetimibe should be tested by reviewing the combined cancer results from the SHARP and IMPROVE-IT trials of ezetimibe, and reporting on the overall findings to the relevant regulatory authorities, independently of the drug manufacturers.

The two hypothesis-testing trials (SHARP and IMPROVE-IT) contain about four times as many cancers as the SEAS trial. They do not confirm the hypothesis raised by the SEAS trial that treatment increases the overall risk of developing cancer. In addition, there is no increase with time in the relative risk (active vs placebo) suggested by the cancer incidence and mortality from all 3 trials together (or just from the pair of hypothesis-testing trials). Consequently, the SEAS, SHARP and IMPROVE-IT trials do not provide credible evidence of any adverse effect on cancer.

Allocation to 5 years of substantial LDL-cholesterol lowering by a statin has been shown previously to have no apparent effect on cancer. The Cholesterol Treatment Trialists' collaboration has published results (Lancet 2005;366: 1267-78) based on 90,000 patients randomised evenly between statin and control. Based on 5530 patients with cancer onset after randomisation, the statin vs control relative risk was 0.997 (with 95% confidence interval 0.95-1.05; not significant). Of these patients, 2163 died of their cancer during the scheduled follow-up period; the relative risk for cancer death was 1.01 (with 95% confidence interval 0.91-1.12; not significant).

In the final results from the SEAS trial, there appears to be a small increase in total cancer incidence in the group allocated ezetimibe + statin, but this is based on only 102 vs 67 cancer cases (including 39 vs 23 fatal cases) and there is no significant increase in any particular type of cancer.

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Two other large trials of ezetimibe + statin are still in progress: (i) SHARP (ezetimibe + simvastatin vs placebo in 9,000 patients; recruitment completed, but treatment and follow-up continuing) and (ii) IMPROVE-IT (ezetimibe + simvastatin vs placebo + simvastatin in 11,000 patients; recruitment continues towards an eventual target of 18,000 patients). Together, they have already accumulated about four times as many cancers as SEAS (see table). If treatment really did increase total cancer by 50% then this would have been clearly apparent in the hypothesis testing SHARP & IMPROVE-IT trials. Instead, there was no evidence of any increase in cancer (see table).

Cancer events	Active	Control
Hypothesis generator: SEAS	102	67
Hypothesis test: SHARP & IMPROVE-IT*	313	326

* 216 active vs 254 control non-fatal cases and 97 vs 72 fatal cases.

If there were a real adverse effect on cancer incidence or cancer mortality then previous experience with the epidemiology of cancer (ie, with other causes of the disease in humans) strongly suggests that the relative risk (active versus control) should grow bigger with time, but it does not, whether the hypothesis-testing trials are considered separately or all 3 trials are considered together.

Note: The University of Oxford Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) has decades of experience in cancer epidemiology, in vascular and other trials, and in collaborative meta-analyses of trials. Although CTSU is conducting the SHARP trial, it is doing so independently of the source of funding, and has a policy of not accepting honoraria or consultancy fees. This report to regulatory authorities on the analyses of SEAS, SHARP and IMPROVE-IT was initiated, conducted and interpreted by the CTSU independently of any source of funding.

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For more information, please, refer to the press release issued by the SEAS investigators today.

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