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ACC 2023 – Esperion's outcomes win looks lacklustre

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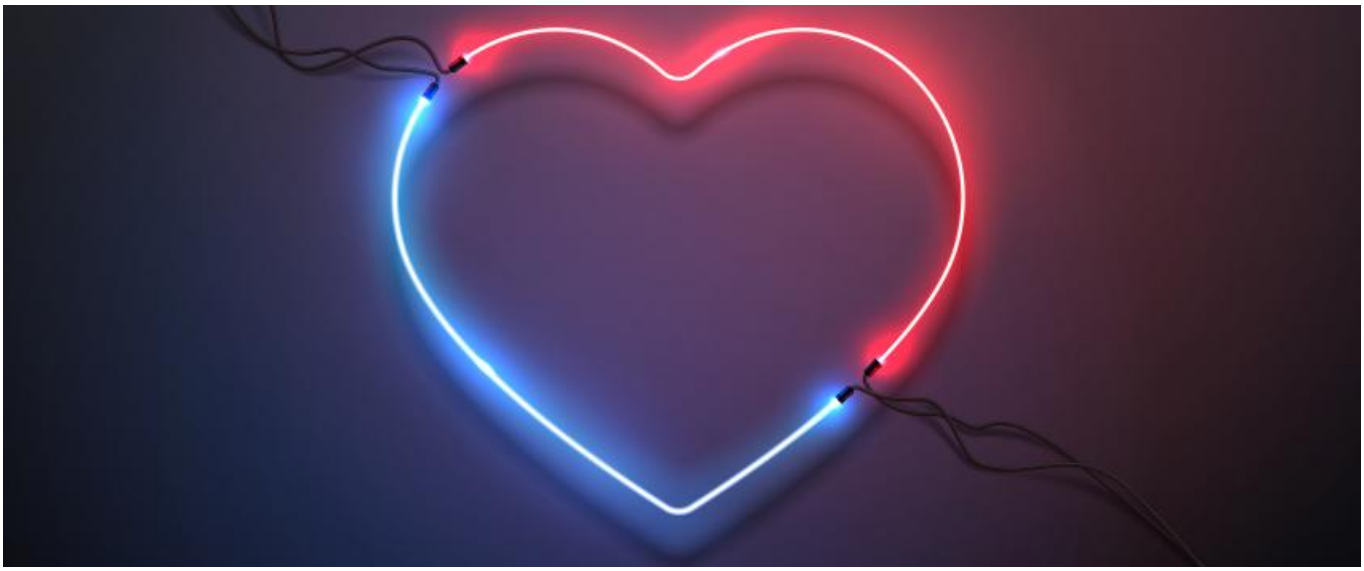

A 13% reduction in the risk of cardiovascular events is statistically significant but not spectacular.

Late last year it looked like fortunes were finally changing for Esperion, which has struggled to launch its cholesterol-lowering pill Nexletol. In December the group revealed that the drug's cardiovascular outcomes trial, Clear Outcomes, had succeeded and that it had bagged a prestigious late-breaker slot at the American College of Cardiology meeting.

Data presented at ACC today and simultaneously published in the *NEJM* show a 13% reduction in the risk of major cardiovascular adverse events (Mace) in patients receiving Nexletol versus those on placebo, a result described in an accompanying editorial as "compelling". However, some had hoped for more.

The study had been 90% powered to detect a 15% reduction in risk of the primary endpoint, so it fell just short of this target. And ahead of the readout BTIG analysts had raised the possibility of a "truly spectacular" 20% reduction.

Nexletol, which contains the active ingredient bempedoic acid, was FDA approved in 2020 for treating high LDL cholesterol in addition to maximally tolerated statins, specifically in patients with heterozygous familial hypercholesterolaemia or established atherosclerotic cardiovascular disease (ASCVD).

Esperion has sought to position the oral drug between statins and injectable PCSK9 inhibitors like Regeneron/Sanofi's Praluent and Amgen's Repatha. Getting a win in Clear Outcomes could boost sales, which have so far been disappointing.

Mace race

The 13% risk reduction was seen on the primary endpoint, a composite of cardiovascular death, non-fatal myocardial infarction or stroke, and coronary revascularisation – also known as Mace-4.

Nexletol looked slightly better on the harder Mace-3 composite, which includes cardiovascular death and non-fatal myocardial infarction or stroke, and was a secondary outcome of the study. Mace-3 is an important endpoint for the EU regulator. In Europe, Daiichi Sankyo is responsible for commercialisation under a 2019 deal that was later expanded to include other regions.

Clear Outcomes also found a reduction in the risk of myocardial infarction and coronary revascularisation, but

there was no impact on stroke or death.

This all makes Nexletol look rather similar to the PCSK9s, although special care should be taken when comparing these cardiovascular outcomes trials because of the differences between them.

For one, the PCSK9s were given on top of statins, while Clear Outcomes tested Nexletol in patients unable or unwilling to take these drugs. Another big difference was that Clear Outcomes enrolled both a primary and secondary prevention population – with a 30:70 split – while the outcomes studies of Praluent and Repatha focused on secondary prevention.

Selected cardiovascular outcome studies			
	Nexletol (Clear Outcomes)	**Repatha (Fourier)**	**Praluent (Odyssey Outcomes)**
N	13,970	27,564	18,924
Population	Statin-intolerant pts with/at high risk of CV disease	Plus statins in pts with CV disease	Plus statins in pts with recent hospitalisation for ACS
Reduction in risk of...			
- Cardiovascular events*	13%	15%	15%
- Mace-3	15%	20%	14%
- Myocardial infarction	23%	27%	14%
- Coronary revascularisation	19%	22%	12%
- Death	NS	NS	NS
Primary endpoints: Clear Outcomes: CV death, nonfatal MI, nonfatal stroke, or coronary revascularisation; Fourier: CV death, MI, stroke, hospitalisation for unstable angina, or coronary revascularisation; Odyssey Outcomes: CV death, nonfatal MI, fatal/nonfatal ischaemic stroke, or hospitalisation for unstable angina. ACS=acute coronary syndrome; Mace-3=CV death, non-fatal MI or stroke; NS=not significant. Source: ACC & NEJM.			

It is the primary prevention setting that could really supercharge Nexletol sales. And interestingly, the primary prevention population in Clear Outcomes performed better on the primary endpoint than the secondary prevention population did – a finding that warrants further investigation, according to the editorial's authors.

Still, they cautioned that it was premature to consider Nexletol as an alternative to statins. Around 10% of patients eligible for statins are unable or unwilling to take them, usually owing to musculoskeletal side effects like pain and cramps. In Clear Outcomes the incidence of myalgia was similar between Nexletol and placebo; however, the Esperion drug was associated with higher rates of gout and cholelithiasis.

Esperion plans to file the data with the FDA and EMA by June, and hopes to have a cardiovascular risk reduction claim on Nexletol's label in the first half of next year. It expects a broad indication covering both primary and secondary prevention, a spokesperson told *Evaluate Vantage*.

At the end of 2022 Esperion had $167m, which should be enough to get it through this year. And the group expects the expanded label to trigger $440m in milestones from Daiichi and Esperion's Japan partner, Otsuka.

The data might be enough to convince regulators. The next big task for Esperion will be convincing cardiologists.

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