

## Event - Glaxo resuscitates hope in darapladib



[Jonathan Gardner](#)

Many investors may have given up on darapladib, but GlaxoSmithKline has not. The novel project failed to keep chronic heart disease patients alive and out of the hospital longer than a placebo in the Stability trial, but executives of the UK group have dropped hints that it could protect against specific cardiovascular events.

Darapladib was brought on board with the buyout of Human Genome Sciences, so Glaxo executives may be keen to prove that the \$3.6bn pricetag was worth it, and hope that regulators will be receptive to any limited benefit given how little progress there has been in this space. It will also be interested to hear views on darapladib's real-world value from cardiologists, before whom Stability benefits will be outlined late this month.

### Data instability

Stability gave a resounding “no” to the question of whether darapladib taken by chronic coronary heart disease (CHD) patients was effective in delaying “major adverse cardiovascular events” (MACE), a composite primary endpoint that encompasses cardiovascular death or non-fatal myocardial infarctions and strokes ([Darapladib failure is a disappointment for a field struggling for direction](#), November 12, 2013).

As Glaxo trailed this disappointing topline result, it also dangled the possibility that certain secondary endpoints might have been met, with complete analysis to be disclosed at a scientific meeting. The data will be presented at a late-breaking trials session at the American College of Cardiology in Washington, DC, on March 30, with further analyses the following day.

Pre-specified secondary endpoints included MACE composites that also included CHD death, hospitalisation for unstable angina or revascularisation procedures; the time to individual components of MACE rather than the composite measures; and all-cause mortality.

In other words, Glaxo gave itself many opportunities to show some type of benefit. If any of them are met, the question will be how important cardiologists view the benefit and, of course, whether it will be sufficient for regulators even to accept an application.

### Give me a hand

The latter point might have been partially answered by the precedent set by the FDA and EMA in accepting Novartis' serelaxin (RLX030) application.

That project managed to return mixed pivotal trial results in heart failure, yet the FDA saw fit to give it breakthrough therapy designation since it did reduce mortality ([Serelaxin continues charmed life with breakthrough designation](#), June 21, 2013). An advisory panel will meet next week to vote on serelaxin; the EMA's counterpart committee has already voted against.

The argument in favour of backing a product with limited benefit is that since the launch of statins in the 1990s very few new drugs have managed to alter the course of CHD. In addition to primary prevention – delaying the onset of heart disease in patients with high cholesterol – statins have a secondary prevention role once symptoms like angina set in. Since darapladib was given on a background of statin therapy in Stability an improvement on any secondary endpoint would probably reflect a real world benefit.

Meanwhile, a win on secondary endpoints could also be a sign that a second trial in acute coronary syndrome, Solid-Timi 52, has a chance of success. ACS is a sicker and more underserved population – patients in Solid-Timi must have had a heart-related hospitalisation in the previous 30 days and angioplasty when possible – and as with Serelaxin in heart failure the FDA could be tantalised by the promise of a new option.

ACS has felled more than one promising new drug in recent years, with the FDA having knocked back Xarelto twice. Of course, as an anticoagulant Xarelto carries bleeding risk, something that could benefit darapladib, which acts on arterial plaque, when it comes to an all-cause mortality endpoint, for example.

Darapladib remains a controversial yet intriguing project, and many analysts have refused to write it off entirely, as witnessed by the modest sales forecasts – *EvaluatePharma's* consensus sits at \$327m in 2018 – that remain in spite of pivotal failure. The analysts at Deutsche Bank perhaps summed it up best when they

wrote this month: “In theory this is a multi-blockbuster drug but the failure to meet the primary endpoint in Stability may entail additional costly (and likely time-consuming) development.”

So even if a surprisingly positive signal is revealed next week, in all likelihood darapladib would remain on a long and expensive path to market.

<b>Trial</b>	<b>ID</b>
Stability	NCT00799903
Solid Timi-52	NCT01000727

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