Evaluate Vantage

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Asset resuscitation fails to resuscitate Mereo

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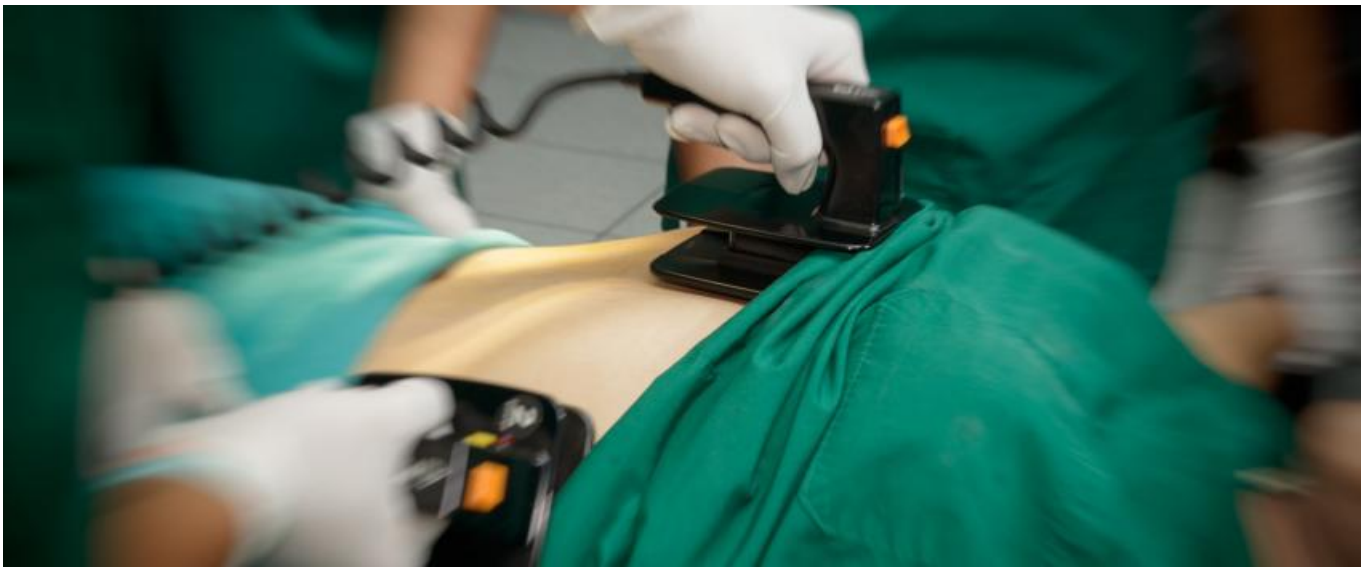

Mereo claims another success with a big pharma castoff, but its win in alpha 1-antitrypsin deficiency is questionable.

Sitting on an 80% 12-month share price decline and trading below its £85m ($111m) of first-quarter cash Mereo is desperate for good news. It was hoping to deliver some today, claiming a success in a mid-stage study of alvelestat, a rare lung disease project earlier discontinued by Astrazeneca.

That said, the sceptical investor will instantly zero in on the fact that Mereo's analysis excludes 15% of patients enrolled, and that there is a possible toxicity signal, with one case of liver enzyme elevation. Most important is that the trial, curtailed during the Covid pandemic, has only tested alvelestat's effect on biomarkers, with nothing known yet about its effect on lung function.

To be fair, Mereo is no different in this regard from its competitors in treating the lung disease in question, alpha 1-antitrypsin (AAT) deficiency. Rival mid-stage projects from Arrowhead/Takeda (ARO-AAT) and Vertex (VX-864) primarily test for increases in AAT levels.

Biomarker strategy

Mereo's phase 2 Astraeus study, enrolling AATD subjects into high and low-dose and placebo cohorts, initially had a sole primary endpoint of 12-week change in plasma desmosine. Two further analyses – change in neutrophil elastase activity and Aα-val360 levels – were later promoted to primaries "to support ... a biomarker development strategy" geared towards accelerated approval.

It is the second two that today gave Mereo the biggest reasons for cheer, showing reductions that yielded p values of <0.05 versus placebo favouring the high alvelestat dose. The low dose also scored on the neutrophil elastase activity metric (alvelestat is a neutrophil elastase inhibitor), but not on Aα-val360.

As for desmosine levels, these fell in response to high-dose alvelestat while increasing in placebo recipients. While the difference appeared to show a numerical benefit at eight weeks, however, none was statistically evident at the 12-week point specified in the protocol.

Does any of this matter? Mereo claims that desmosine and Aα-val360 correlate with lung function and lung density in AATD patients, and decline in response to AAT augmentation, which at present is used to treat the condition. AATD is a rare disease, and an accelerated approval pathway based on surrogate endpoints remains a possibility, at least in theory.

But the FDA's position on the use of biomarkers to back approval will not become clear until a filing is actually

made. Mereo promises to provide data on secondary endpoints, which include the lung function measure FEV_1, in the second half, after which it will decide on the design of a registrational study.

It is also unclear how regulators might view the possible toxicity signal, or whether this presages anything more serious. One high-dose alvelestat subject had alanine transaminase elevation that met study stopping criteria, but Mereo claimed that there were no incidences of Hy's law in Astraeus.

Statistical rigour

The overall rigour of the Astraeus readout might also be questioned. While the trial had initially aimed to enrol 165 patients, a decision was made to close it once 99 subjects were recruited.

One of these 99 was not dosed, and four did not have at least one measurement of a primary endpoint after baseline. A further 10 patients were then excluded because they had moderate/severe acute exacerbations, something that increases Aα-val360 and desmosine in AATD patients.

Though Mereo made the last change before unblinding, intending to "reduce noise" in the now curtailed trial, the fact remains that the data released today relate to 84 per-protocol patients, and nothing is known about alvelestat's effect on a strict intent-to-treat basis.

Mereo stock fell 20% this morning, suggesting that investors remained unconvinced. Though Mereo has once before managed to sell on a discontinued asset at an apparent profit, there is little to suggest that Astra regrets letting alvelestat go just yet.