Evaluate Vantage

March 06, 2023

ACC 2023 – Merck reaches for the stars

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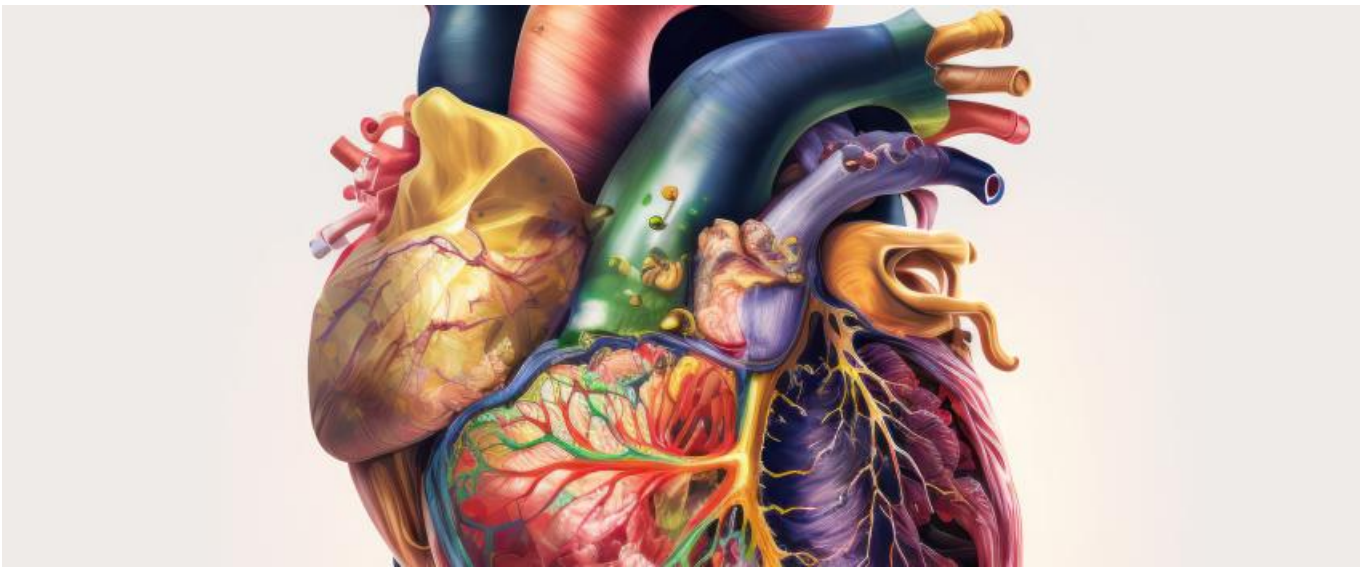

The Stellar trial of sotatercept lives up to its name, but the asset did not come cheap.

Merck & Co has for a while now been using highly positive language to hint at the outcome of the pivotal Stellar trial of its pulmonary arterial hypertension project sotatercept. In retrospect it has been quite moderate: the data, presented today at the ACC meeting, are pretty sensational.

They put the company on course to have the first therapy for this disease that might be regarded as disease modifying. Regulatory submissions are imminent, but even if approval does come sotatercept sales will also need to impress to vindicate the $11.5bn Merck spent on Acceleron, sotatercept's originator, in 2021.

Currently approved PAH therapies essentially work as vasodilators, relieving hypertension and thus pressure on the heart. Sotatercept, an activin receptor fusion protein, is designed to bind to activin A, thereby decreasing proliferation of cells in the pulmonary artery walls, treating the underlying arterial stiffening that causes PAH in the first place.

"The results that we see are not due to vasodilation, as with all other established drugs," says Joerg Koglin, Merck's vice-president of clinical development. "We see a strong effect. We see, really importantly, also, strong unloading of the right side of the heart."

This pattern suggests that sotatercept might be working at a more fundamental level than the vasodilators.

Walk the line

Stellar's primary outcome was exercise capacity, as measured by mean change from baseline at week 24 in the six-minute walk distance (6MWD). Sotatercept recipients beat those given placebo by 40.8m on this measure, trouncing even the most optimistic analysts' expectations, which were hovering at around the 30m mark. the placebo-adjusted median difference in 6MWD with sotatercept was 34.4m; the biggest selling PAH drug, United Therapeutics' inhaled prostacyclin Tyvaso, achieved a placebo-corrected median change in peak 6MWD of 20m after 12 weeks' treatment.

The trial employed an unusual statistical analysis: the HL location shift, or Hodges-Lehmann estimate, of the difference between the sotatercept and placebo groups. This corrects for outliers and imputes missing data, for example from those who died before the trial ended and thus for whom no 6MWD figure was available, Koglin explains. The Hodges-Lehmann estimate measure was agreed by the FDA, so should be a valid basis for an approval decision.

Stellar (NCT04576988) data		
	Sotatercept vs placebo	
Efficacy endpoint	**Benefit**	**P value**
Six minute walk distance (m)*	40.8^	<0.001
Multicomponent improvement (%)**	28.8	<0.001
Pulmonary vascular resistance (dyne-second per cm5)	-234.6^	<0.001
NT-proBNP (pg/mL)	-441.6^	<0.001
WHO functional class (%)	15.6	<0.001
Time to all-cause death or clinical worsening	HR=0.16^	<0.001
French low-risk score (%)	21.3	<0.001
PAH-Sympact physical impacts	-0.26^	0.010
PAH-Sympact cardiopulmonary	-0.13^	0.028
PAH-Sympact cognitive/emotional	-0.16^	0.156

**Primary endpoint. **Defined as meeting all 3 of the following at week 24: increase of ≥30m in 6MWD; decrease of ≥30% in NT-proBNP level or maintenance/achievement of NT-proBNP level <300 pg/ml; and shift from class III to II or I, or class II to I in WHO FC, or maintenance of class II. ^According to HL location shift. Source: ACC & NEJM.*

It will not hurt that sotatercept hit eight out of the nine sequentially analysed secondary efficacy endpoints. Of these, time to death or clinical worsening is one of the most important.

“The hazard ratio of 0.16 equates to an 84% reduction in the time to death or the first non-fatal clinical worsening event,” says Koglin. “That is an enormous reduction. That has not been seen in any other PAH studies.”

Safety was also acceptable. There were more adverse events related to treatment with sotatercept – 47.2% versus 26.9% with placebo. But on serious adverse events related to treatment, slightly more were seen in the placebo group than among those given Merck’s agent.

Adverse events that occurred more frequently with sotatercept than with placebo included nosebleeds, dizziness and spider veins.

Enough?

Sotatercept is surely heading for approval, probably in the back half of this year. Sales forecasts are respectable, with *Evaluate Pharma* compiling a 2028 consensus forecast of $1.4bn, though this figure will probably swell in the coming weeks. The agent’s NPV is currently calculated at $4.8bn.

But sotatercept was one of the two main products behind Merck’s acquisition of Acceleron. The other, the blood disorder therapy Reblozyl, has an NPV of $7.2bn, but only $1.5bn of this is expected to accrue to Merck. As positive as the Stellar data are, Merck still has a lot of work to do to make its money back.