Evaluate Vantage

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AHA 2022 – Amgen looks good in metabolic disease

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With a mid-stage win in cholesterol lowering in the bag, attention turns to obesity.

Data on Amgen's cardiovascular disease project olpasiran, presented yesterday at the AHA meeting, look pretty good, positioning the small interfering RNA ahead of Novartis's similarly acting pelacarsen on a cross-trial basis.

But another, possibly more important catalyst for the stock is on the horizon. Data on AMG 133, Amgen's obesity candidate, are due in the first week of December. Following a big analyst upgrade to Amgen's stock, partly on the back of this project, expectations are at fever pitch – so much so that some are asking whether these expectations can in fact be met.

Results from the phase 2 Ocean(a) Dose trial of olpasiran (AMG 890) showed that when dosed at 75mg and above for 36 weeks, the agent lowered levels of lipoprotein(a) by at least 94%. Given that the placebo group saw their lipoprotein(a) levels rise, the placebo-adjusted figures show that two dose levels of olpasiran lowered lipoprotein(a) by more than 100%.

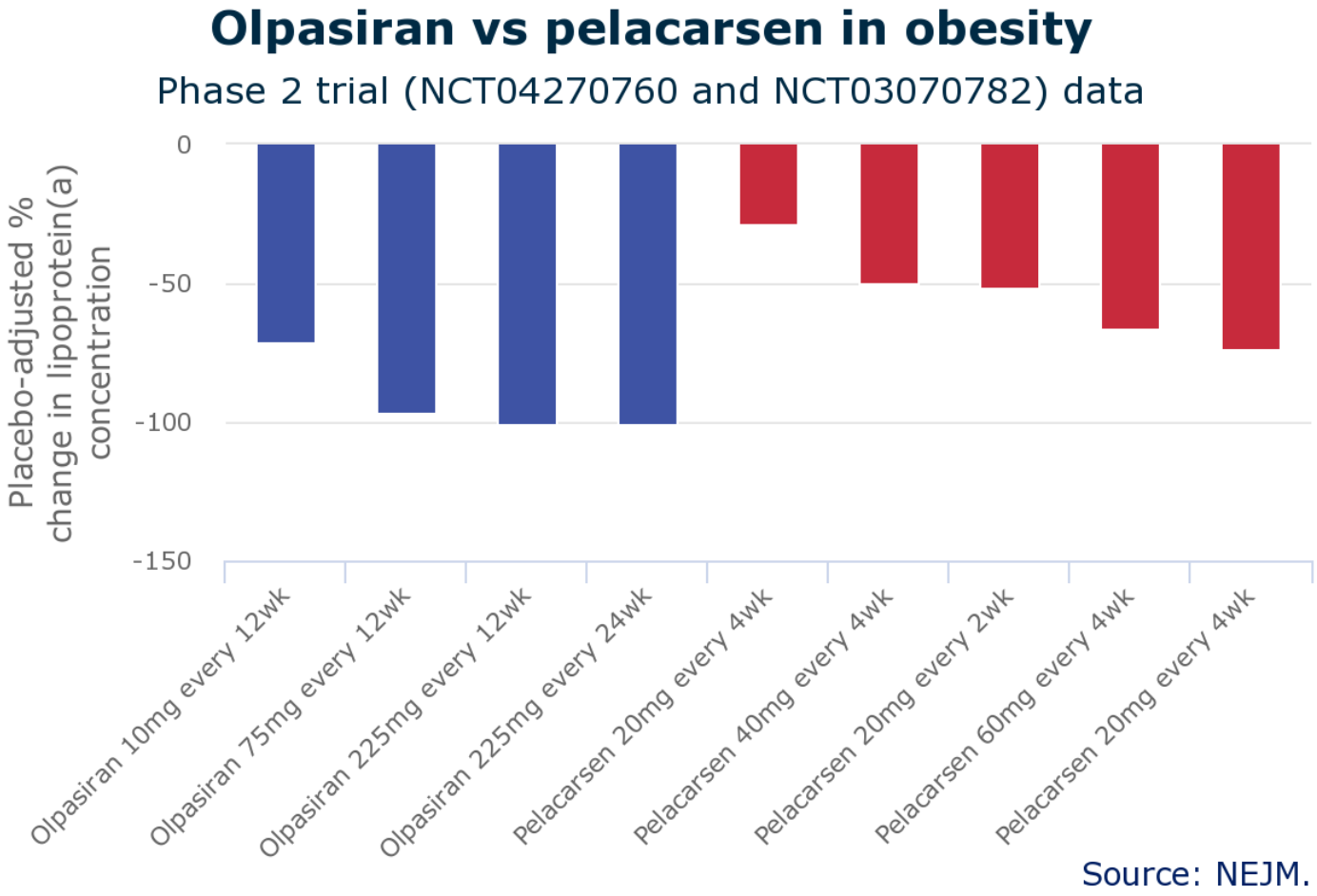
Reductions in LDL cholesterol and apolipoprotein B were also seen.

Ph2 Ocean(a)-Dose study data					
	Placebo	Olpasiran			
	Q 12 Wk (N = 51)	10 mg q 12wk (N = 57)	75 mg q 12wk (N = 57)	225 mg q 12wk (N = 53)	225 mg q 24wk (N = 53)
% change in lipoprotein(a) concentration	4	-67	-94	-98	-97
Pbo-adj % change in lipoprotein(a) concentration	-	-71	-97	-101	-101
% change in LDL cholesterol concentration	6	-17	-16	-17	-19
Pbo-adj % change in LDL cholesterol concentration	-	-24	-23	-23	-25
% change in apolipoprotein B concentration	7	-12	-9	-10	-11
Pbo-adj % change in apolipoprotein B concentration	-	-19	-17	-18	-19
Source: NEJM.					

A comparison with results of the phase 2 trial of Novartis's pelacarsen puts olpasiran ahead on lipoprotein(a) reductions, the primary efficacy endpoint of both trials. Novartis has taken an 80mg monthly dose of the antisense oligonucleotide into its pivotal Lp(a)Horizon trial, results of which are due in 2025. The two projects have slightly different mechanisms: pelacarsen, originated by Ionis, is an antisense/GalNAc conjugate designed to reduce lipoprotein (a), whereas olpasiran, which Amgen licensed from Arrowhead, is a small interfering RNA.

Of the two, Amgen's project has the dosing advantage. Novartis's oligonucleotide is administered monthly, whereas in Ocean(a) Dose olpasiran was given subcutaneously every three months; there was even an every six months arm which showed highly respectable results.

Amgen's phase 3 trial, Ocean(a) Outcomes, is to start this year with data expected in 2027. The doses have not yet been revealed, but olpasiran will again be given every three months.



There are, however, other competitors here. Silence Therapeutics' SLN360, also a siRNA, has not yet entered phase 2, but in phase 1, a single 300mg and 600mg dose decreased lipoprotein(a) levels by 70% and 81% respectively at five months. A phase 2 trial assessing three dose levels is set to start by the end of the year.

And Lilly/Dicerna's LY3819469, a GalXC RNAi candidate targeting the LPA gene is also in phase 2. Dicerna was acquired by Novo Nordisk last year.

All of this makes for interesting reading, but it is worth remembering that lipoprotein(a) reduction is by no means a hard endpoint. The NEJM paper on the Ocean(a) Dose data states, "it remains unclear how much of a reduction in the lipoprotein(a) concentration would be necessary to translate into a meaningful reduction in the risk of cardiovascular events".

Obesity data

With phase 3 results on olpasiran some way off, Amgen investors can turn to another forthcoming readout. Data from the phase 1 obesity trial of AMG 133, the group's GIP receptor antagonist/GLP-1 agonist, are set to be released at the World Congress on Insulin Resistance, Diabetes and Cardiovascular Disease in the first week of December.

Analysts at Morgan Stanley upgraded Amgen last month, saying that AMG 133 could achieve a similar degree of weight loss to Lilly's Mounjaro, possibly with a longer duration of effect. This contributed to a 6% jump in Amgen shares, adding a cool $7bn to its market cap as a result.

Exactly what data the Morgan Stanley analysts had seen is not clear. The only clinical update known to have come on AMG 133 was at Amgen's business review in February, where it said that the project had allowed dose-dependent weight loss of up to 8kg in obese patients. The time cutoff for this data is unknown.

Lilly's Mounjaro achieved weight loss of up to 24kg at 72 weeks in the phase 3 Surmount-1 trial, and Novo Nordisk's Wegovy managed around 15kg at 68 weeks in Step-1, also a phase 3 obesity trial.

On Amgen's third quarter earnings call last week, David Reese, vice-president of R&D, said that the things to look out for in the full phase 1 data were dosing and dosing interval, speed and sustainability of weight loss, and overall tolerability.

This prompted analysts from Wolfe Research to strike a note of caution. They wrote that Amgen seemed to be de-emphasising the magnitude of weight loss, which would be most investors' number-one concern, with tolerability being number two.

Amgen is planning a phase 2 trial of AMG 133, so presumably the upcoming data are good enough to justify that move. But the extent of the weight loss will be scrutinised carefully.

This story has been updated to clarify the origins of olpasiran and pelacarsen.