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Event – Key moment for Medicines Company's transformation

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The Medicines Company's decision to cancel MDCO-216, its number two cardiovascular project, amplifies the need for its cholesterol-lowering agent PCSK9si to meet expectations when full data are revealed next week.

Readout of the Orion-1 trial at the American Heart Association meeting will allow physicians and potential partners to assess its potency in lowering LDL cholesterol (LDL-C), as well as comparing it against marketed agents like statins, and PCSK9 inhibitors such as Praluent and Repatha. If it is unequivocally positive, the New Jersey-based group enters a deal-making phase, as it will almost certainly need a big pharma partner or buyer to carry out the massive trials necessary to confirm a benefit in long-term outcomes.

The hunter

The company has already given a preview of data from Orion-1, announcing that in an interim analysis, PCSK9si (ALN-PCSsc) had confirmed "significant and durable" reduction in LDL-C 90 days after treatment – similar to what had been found in an earlier phase I trial. That phase I trial found a 44% reduction in LDL-C 140 days after a single injection of the RNAi candidate (*ESC – PSCK9 space may need to make room for RNAi, August 31, 2015*).

Company	The Medicines Company
Product	PCSK9si (ALN-PCSsc)
Market cap	$2.3bn
Product NPV	$281m
% of market cap	12%
Event type	Phase II data
Date	November 15, 2016

Full Orion-1 data will be disclosed as a late-breaker at AHA.

PCSK9si targets PCSK9, a protein that reduces the number of receptors in the liver that assist in the removal of LDL in the bloodstream. It follows a similar pathway as Amgen's Repatha and Sanofi and Regeneron's Praluent, which are antibodies that bind to PCSK9 in the bloodstream.

As an RNA-modulating agent that impedes PCSK9 synthesis in cells, Medicines Company's project has the potential to reduce injections to two or four times a year, versus once every two weeks or a month for Praluent and Repatha. Orion-1 tested several doses of PCSK9si on a quarterly or twice-yearly schedule – as the company has argued, infrequently enough that each injection could coincide with a regular physician visit (*Interview – Medicines Company looks away from the hospital bed, September 8, 2015*).

Repatha and Praluent achieved regulatory approval on LDL-C reductions of up to around 60%, depending on the study and population tested, providing a benchmark against which PCSK9si can be compared. Of course, with its dosing schedule and the potential to do it in conjunction with regular physician visits, Medicines Company could build a pharmacoeconomic case around lower frequency and better adherence.

And, of course, all these claims would need to be backed up by long-term outcomes – Praluent and Repatha are nearing readout for both of their massive trials attempting to prove that they can prevent death and cardiovascular events (*Amgen starts to gain upper hand in PCSK9 battle, February 3, 2016*).

The outcomes data are necessary for approval in a broad patient population that cannot control LCL-C using statins alone. However, regulators have okayed Praluent and Repatha in high-risk patients and those with

genetically linked high cholesterol on the LDL-C endpoints alone, and PCSK9si should be able to do the same if phase II biomarker results are confirmed in phase III.

The Italian job

Medicines Company's second cardiovascular shot on goal had been MDCO-216, a recombinant ApoA-1 mutant. This protein, which mimics LDL-scavenging high-density lipoprotein, had been discovered in residents of an Italian village in which some people had little atherosclerotic build-up despite exceptionally low HDL levels and elevated levels of harmful triglycerides.

Results from a trial of MDCO-216, using intravascular ultrasound findings as a primary endpoint, are also on the agenda as an AHA late-breaker. However, after reviewing the data the company announced late yesterday that it was discontinuing this project because it did not show a sufficient effect on atherosclerotic plaque; shares fell 6% after market.

The group was quick to emphasise that cessation of MDCO-216 would make more cash available to advance PCSK9si. This makes it even more crucial for the latter project to meet expectations.

Project	Study	Trial ID
PCSK9si	Orion-1	NCT02597127
MDCO-216	Milano-Pilot	NCT02678923

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