Evaluate Vantage

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ACC 2022 – Astra's cholesterol lowerer surprise comes just a little late

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A little-known antisense oligonucleotide, Astrazeneca/Ionis's AZD8233, has surprised in a mid-stage trial, showing cholesterol lowering well in excess of Amgen and Sanofi/Regeneron's anti-PCSK9 MAbs and Novartis's RNAi therapy Leqvio. 50mg once monthly, the middle of three AZD8233 doses tested in the Etesian study, prompted 73% LDL cholesterol reduction from baseline at 12 weeks, the ACC meeting heard yesterday. Astra had licensed AZD8233, a subcutaneously dosed inhibitor of PCSK9 expression, from Ionis back in 2016, five years before the companies tied up over eplontersen. The group played up AZD8233's best-in-class efficacy and monthly dosing convenience; Leqvio is given every six months, but on a cross-trial basis appears less efficacious. Still, the real threat could come not from established anti-PCSK9s but from Merck & Co's investigational MK-0616, which not only is given orally but also has shown LDL-C lowering of around 65%. A further caveat is safety: some patients given AZD8233 90mg experienced liver enzyme elevations. Two other phase 2 AZD8233 trials, the 28-week Solano study and Hyate, a Japan trial, are due to read out later this year.

Convenience and efficacy in PCSK9 inhibition

Product/project	Company	Description	Dosing	LDL-C lowering
Marketed				
Leqvio (inclisiran)	Novartis	SC anti-PCSK9 RNAi	Twice-yearly SC	50-52%
Repatha	Amgen	SC anti-PCSK9 MAb	Two-weekly SC	55%
Praluent	Sanofi/Regeneron	SC anti-PCSK9 MAb	Two-weekly SC	58%
Phase 2				
MK-0616	Merck & Co	Oral anti-PCSK9	Once-daily oral	~65%
AZD8233	Astrazeneca/Ionis	SC anti-PCSK9 antisense	Monthly SC	73%*

*All on top of background statins; Repatha, Praluent & Leqvio data placebo-adjusted; SC=subcutaneous; IV=intravenous; *middle, 50mg dose. Source: product labels, AHA 2021 & ACC 2022.*