NEWS IN BRIEF

PCSK9 inhibitor space starts to heat up

A slew of results on lipid-lowering PCSK9-targeting mAbs, presented at the annual American College of Cardiology meeting in Chicago, highlighted one of the next big hopes for cardiologists.
The lowdown: Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease that binds low-density lipoprotein (LDL) receptors, leading to their degradation and a subsequent increase in LDL-cholesterol (LDL-C) levels. In part because loss-of-function *PCSK9* mutations reduce the risk of coronary heart disease and because gain-of-function mutations are linked to hypercholesterolaemia, many drug developers are working on strategies to inhibit PCSK9 activity (see the Review on page 367).

Leading the pack are Regeneron and Sanofi, which presented data from two Phase II trials of their monoclonal antibody (mAb) REGN727 (also known as SAR236553). Their trials cumulatively enrolled over 270 patients with primary hypercholesterolaemia who were already taking statins, and different doses of the drug tested on different schedules reduced LDL-C levels by 35–67% after controlling for placebo. Amgen also presented data from a 51-patient Phase I trial of AMG145. Patients with hyperlipidaemia on statins who were treated with AMG145 experienced 63–81% reductions in LDL-C levels compared with placebo-treated patients. "Both drugs showed strong efficacy signals and positive safety profiles and represent the emergence of a promising new therapeutic class," wrote BioMedTracker analysts in a comment.

A key outstanding question now is whether success on the surrogate LDL-C end point will correlate with real improvements in cardiovascular health. Regeneron and Sanofi started a 2,100-patient Phase III trial of REGN727 for high-cardiovascular-risk patients with hypercholesterolaemia in February. Amgen has pushed AMG145 into Phase II trials, and anticipates results from these later this year. Other anti-PCSK9 mAbs in Phase II development include Novartis's LGT209 and Pfizer's RN316.

Earlier in the year, Bristol-Myers Squibb and Isis discontinued development of their Phase I antisense anti-PCSK9 candidate BMS-PCSK9Rx, citing regulatory concerns about the target. Regeneron has said the concerns raised by the US Food and Drug Administration (FDA) are "theoretical" and in line with the typical drug development process.

Interleukin-17 double take

Biologics that target the interleukin-17 pathway yield promising Phase II plaque psoriasis results, show a pair of studies.
The lowdown: Interleukin-17 (IL-17) was identified in 1993 and has since become an attractive therapeutic target on the basis of its role as a key pro-inflammatory cytokine. The most clinically advanced IL-17-targeted therapy is Novartis's secukinumab — which is in Phase III development for plaque psoriasis, psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis — but other companies with candidates in development include Lilly, Amgen, Roche and Abbott. Recently published results of Phase II studies from two of these underscore the promise of the class.

In a trial sponsored by Lilly, 142 patients with plaque psoriasis were treated with different doses of the IL-17-targeting mAb ixekizumab or placebo. The three highest doses met the primary end point, inducing 75% improvements in psoriasis area and severity index (PASI) scores in 76–83% of patients by week 12, compared with only 8% of placebo-treated patients (*N. Engl. J. Med.* **366**, 1190–1199; 2012). Amgen, by contrast, randomized 198 patients with plaque psoriasis onto treatment with its IL-17 receptor-targeting brodalumab or placebo, and met its slightly different primary end point of an average PASI improvement at 12 weeks (*N. Engl. J. Med.* **366** 1181–1189; 2012). The different doses of brodalumab induced improvements of 45–86%, compared with 16% for placebo-treated patients.

"Few adverse effects were observed, and few patients withdrew from the trials," notes Ari Waisman from the University Medical Center of the Johannes-Gutenberg University in Mainz, Germany, in a linked editorial (*N. Engl. J. Med.* **366**, 1251–1252; 2012). Although anti-TNF (tumour necrosis factor) treatments have "fundamentally improved therapeutic options for patients with autoimmune diseases", he adds, side effects of these include severe infection and have limited their utility. "Treatment with antibodies targeting IL-17 or its receptor should be more specific and may be expected to result in fewer side effects and therefore hold promise for patients with psoriasis," he concludes.

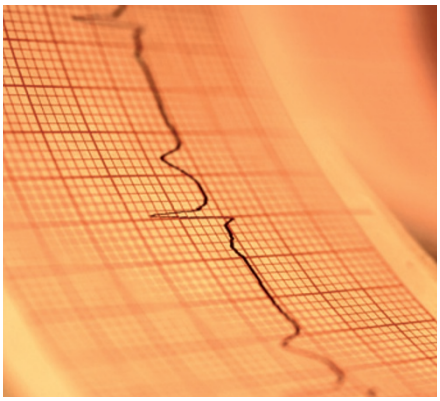
Lilly initiated Phase III development of ixekizumab late last year, and Amgen plans to start pivotal trials of brodalumab later this year. Roche's and Abbott's candidates are in Phase I development.

More CV data needed for obesity drugs, says panel

An FDA advisory panel votes in favour of the need for cardiovascular outcome data for obesity drugs.
The lowdown: Obesity drugs were back in the spotlight as the FDA's Endocrinologic and Metabolic Drugs Advisory Committee met for two days to discuss the regulatory requirements for obesity drugs. At issue was what kind of cardiovascular (CV) safety data should be needed to secure approval for obesity drugs. Given the chequered history of previously approved agents, the independent advisors voted 17–6 in favour of CV outcomes studies for agents that do not seem to have CV risk. The panel did not vote on the requirements for agents that show theoretical or preclinical CV risk.

Discussions around the design of such outcomes studies raised the possible need to double the size of Phase II and III programmes and enrich for high-risk patients. An industry representative told panellists that these requirements could add US$100 million to the cost of obesity drug development.

FDA officials have said it is "unlikely" that the vote will affect the review of two drugs that have been filed with the FDA. Earlier this year, the panel recommended approval for Vivus's Qnexa (phentermine plus topiramate). The FDA has extended the review timeline for Qnexa by 3 months, until mid-July. The panel is due to meet again this month to discuss Arena's lorcaserin, ahead of an anticipated regulatory decision on the drug by the end of June.



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