IN brief

Spinal device cancer risk

Medical device maker Medtronic is under investigation by the US Senate Finance Committee, a group of spine specialists and media outlets for its financial ties to doctors who downplayed serious side effects of the company's recombinant bone growth treatment. In 13 clinical studies, doctors did not link adverse events such as sterility, infection and bone loss to Infuse, a product used in spinal fusion surgery, according to research published in the June 2011 issue of *The Spine Journal*. The doctors were also aware of, and did not report, critical information linking a stronger dose of the drug to cancer, according to an October media review of Food and Drug Administration documents. The Senate committee has demanded that Medtronic, based in Minneapolis, turn over records of communication with and payments to the doctors who authored the clinical studies. The doctors were paid a median of \$12 million to \$16 million each over ten years in consulting and royalty fees for various Medtronic products. "With those numbers you can be sure you've got a surrogate marketing department," says Arthur Caplan, director of the Center for Bioethics at the University of Pennsylvania in Philadelphia. Infuse, a recombinant form of the protein BMP-2 (bone morphogenetic protein-2) approved by the FDA in 2002 earned Medtronic \$900 million in its most recent fiscal year. The company in August gave \$2.5 million to Yale University researchers to oversee reviews of all BMP-2 clinical data.

Emily Waltz

\$352 million into microRNA

MicroRNA (miRNA) company Miragen Therapeutics of Boulder, Colorado, entered a \$352 million licensing and development agreement with French pharma Servier Laboratories of Suresnes in October. Miragen will receive \$45 million upfront, and research support and commercial milestones worth ~\$307 million. The total deal value may reach \$1 billion including royalties and product sales. Miragen's programs use Hoersholm, Denmark-based Santaris Pharma's Locked Nucleic Acid Drug Platform to identify and select drug candidates against Miragen's miRNA targets. The agreement with Servier focuses on two defined miRNA targets: miR-208, involved in heart failure pathogenesis and progression, and miR-15/195, involved in cardiomyocyte survival and proliferation. The deal also includes a third, undefined target that can either be taken from Miragen's pipeline or from jointly identified targets for cardiovascular disease in blood samples. "It is a good fit between [our] innovative microRNA technology coupled with [Servier's] well-driven insight into the clinical development," says William Marshall, president and CEO of Miragen. Striking a deal with a mid-size pharma, such as Servier, "gives a little more flexibility," says Bird, "they are less likely to turn the light off if things don't go well."

Sabine Louët

Box 1 Sanofi's shiny new MS franchise

Sanofi could very quickly move from having no MS drugs in its portfolio to having two, following its acquisition last year of Cambridge, Massachusetts-based Genzyme, the developer of alemtuzumab. A humanized cytolytic mAb directed at the CD52 lymphocyte antigen, the drug is better known as Campath, the brand under which Genzyme and Bayer, of Leverkusen, Germany, have long marketed the antibody as a treatment for B-cell chronic lymphocytic leukemia. The mAb's ability to deplete both autoreactive and healthy lymphocytes is thought to allow the immune system to 'reboot' in MS patients. Thus far, alemtuzumab has demonstrated clear superiority at reducing relapses over Rebif (IFN- β 1a), which is marketed by the Merck Serono arm of Darmstadt, Germany-based Merck.

Alemtuzumab is usually administered in two annual treatments, consisting of five infusions over five days in the first year, followed by three infusions over three days a year later. That regimen could offer compliance benefits over chronically administered therapies that are difficult to tolerate. Alemtuzumab has substantial safety hurdles, however. In two phase 3 trials, which were of two-years' duration, it caused thyroid-related autoimmune disease in 16% and in 18% of patients, respectively, although the peak incidence tends to rise to ~30% after two years. "These are pretty predictable events," says Michael Panzara of Genzyme, a great advantage for an area where existing drugs have considerable side effects and many of the novel drugs have mechanisms with adverse event profiles, which have been only partially explored in small cohorts of patients. At this point, patients receiving alemtuzumab, which has been in trials for more than a decade, can be monitored and standard therapies can be started quickly. Less predictable are the long-term effects on the immune system, although recently published patient data (*J. Neurol. Neurosurg. Psychiatry* published online, doi:10.1136/jnnp-2011-300826 (5 November 2011)) show that B-cell populations recover in about a year, whereas CD8⁺ and CD4⁺ T-cell populations can take several years to recover—and in a majority of patients they never get back to baseline levels. "We find that these cells, although at lower levels, remain functioning," Panzara says. "We don't see the types of infections you would worry about when these cell populations are depleted."

Sanofi's oral drug teriflunomide, like BG-12, is largely a known quantity from a safety perspective. Its active ingredient is also the active metabolite of a generic prodrug called leflunomide, which Sanofi used to market as the rheumatoid arthritis drug Arava. Liver damage is the main safety risk. "We would exclude patients with severe hepatic impairment on the basis that we have enterohepatic recycling of the product," says Anita Burrell at Sanofi. Its efficacy appears modest, however, although in two early-stage combination trials, in which it was paired with either Copaxone or IFN- β , the effects seen were highly additive, albeit preliminary. "We did see a numerical reduction in relapses, but we are very cautious about that result," she says. A large phase 3 trial, called TERACLES, which pairs teriflunomide with IFN- β , is now underway, although data will not be available until 2014.

doctors are reaching the stage where they are getting much more comfortable with the safety profile and will start to more actively consider earlier line use," says Emmanuel Papadakis, an analyst at Collins Stewart in London. Even so, Novartis is developing a more selective and, it hopes, safer follow-on compound to Gilenya, BAF312. That molecule only binds two of five S1P receptor subtypes considered relevant in MS—S1P-1 and S1P-5, which are expressed by lymphocytes and by cells of the central nervous system, respectively. It does not interact with the S1P-3 receptor, which is expressed in cardiovascular tissue. "Data presentation has been limited to date, and I haven't seen enough to comment on whether its efficacy or safety

will supersede fingolimod," Papadakis says. Schlieren, Switzerland-based Actelion is also conducting clinical trials of another S1P receptor agonist, ponesimod, which is selective for S1P-1 only.

Although BG-12 is currently winning most mindshare in physician surveys and among investment analysts, given the complexity and unpredictability of MS, its full potential will not become apparent until it has been followed for several years in a large population of patients. As with other MS drugs, it will also function as a probe. How different patients respond to BG-12 could shed further light on the biological underpinnings of the condition.

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