IN brief

Intercept price quadruples in a day

Intercept Pharmaceuticals' value jumped as much as 580% over two days in January following the unexpected announcement that it had stopped a trial of a liver disease drug because the drug's efficacy was so high. Shares in the 45-person, New York-based company soared when interim results with the drug obeticholic acid (OCA) for nonalcoholic steatohepatitis, which involves lipid accumulation in the liver, showed a highly statistically significant improvement. The Data and Safety Monitoring Board made the recommendation to halt the study after reviewing liver biopsy data from about half the 283 patients. "I don't think it was broadly known that there was going to be an interim look," says James Molloy, managing director at Janney Montgomery Scott, pointing out that most early peeks at clinical trial data simply signal that the trial should continue. Patients that hadn't completed the trial were recorded as nonresponders in the intention-to-treat analysis, and the trial still registered a *P*-value of 0.0024 for the drug compared to placebo. "That's a fantastic result," Molloy concluded. The analyst thinks the US Food and Drug Administration will still require another trial to approve OCA in this indication, but he believes part of the run-up in stock price came from the potential for OCA to be used off-label to treat fatty liver, which affects 2–5% of US citizens. Intercept's partner on the drug is Dainippon Sumitomo in Osaka, which is conducting a similar trial in Japan. **Brian Orelli**

IN their words

"It's a modest acknowledgment of the fact that learning from a doctor who is paid by a drug company to give a talk about its products isn't the best way for doctors to learn about those products," Jerry Avorn of Harvard Medical School, commenting on GlaxoSmithKline's announcement that it will end its practice of paying doctors to promote its drugs. (*The New York Times* 16 December 2013)

"In the UK, the science is world-class. But in Boston, there is a compounding factor where the science meets experienced entrepreneurs and a much larger pool of venture capital investors and public investors, which usually leads to a greater number of successful outcomes." Otello Stampacchia, an investment adviser at venture-capital firm Omega Funds in London, explains why the UK biotech hub is losing biotech jobs to Boston. (*Bloomberg News* 22 January 2014)

"This high court, which gave corporations the ability to patent life forms in 1980, and under Citizens United in 2010 gave corporations the power to buy their way to election victories, has now in 2014 denied farmers the basic right of protecting themselves from the notorious patent bully Monsanto." Jim Gerristen, a Maine organic farmer, commenting on the US Supreme Court's decision to uphold a lower court ruling to grant Monsanto the right to sue farmers for patent infringement. (*Legal Newsline* 22 January 2014)

clinical remission. Just 16% of those who had initially responded to the drug but who had then crossed over into the placebo arm remained in remission. "Every clinical trial that's ever been performed with this agent [in ulcerative colitis] has been statistically significant," Feagan says.

In Crohn's disease the results are less compelling. The drug failed to meet the primary endpoint of one of two induction trials. This may have been owing to the timing of the assessment rather than the efficacy of the drug, a possibility raised by the FDA panel. The heterogeneity of Crohn's and the disease severity of the patients recruited onto the Crohn's trials may also have been factors. In contrast to ulcerative colitis, which is limited to the colon and the rectum, and which involves inflammation of the surface mucosa only, Crohn's can occur anywhere from the mouth to the anus, and it involves inflammation of the entire gut wall. Moreover, Takeda's Crohn's trials enrolled a higher percentage of patients who had failed one or more tumor necrosis factor- α (TNF- α) inhibitors than its ulcerative colitis trials did.

Nevertheless, the drug did hit the endpoint of a follow-up maintenance study. After a year, clinical remission was achieved by 39% of patients who took Entyvio every 8 weeks (Q8W) and 36.4% of those who took it every 4 weeks. Only 21.6% of those who initially responded to the drug, and then crossed over into the control arm, remained in remission. The difference between each of the drug treatment arms and the control arm was statistically significant (Q8W *P* = 0.0007; Q4W *P* = 0.0042). "What's really important in this, in the long run, is long-term maintenance," Parikh says.

So far, TNF- α inhibitors are the only class of biologic drugs to have gained widespread use in IBD therapy. Around two-thirds of patients respond initially, but a majority lose their response over time. It's an open question whether Entyvio represents a better option—but it's one which Takeda may address with a head-to-head study. "We absolutely are considering that right now," Parikh says. In the meantime, the most obvious early adopters of Entyvio are those who have failed one or more TNF- α inhibitors. "The unmet need is probably largest among those who have run through their options," he says.

Several other firms are also developing integrin-targeting drugs, with mechanisms

similar to that of Entyvio (Table 1). Pfizer, of New York, aims to achieve a similar but reverse effect to that of Entyvio by targeting the ligand of $\alpha 4 \beta 7$ integrin, MAdCAM-1, with an antibody called PF-00547659. Ajinomoto Pharmaceuticals, of Tokyo, has tested a small-molecule inhibitor of integrin $\alpha 4$, which, presumably, has a similar mechanism to that of Tysabri in both Crohn's and ulcerative colitis patients. (One publication describing its activity was later withdrawn because of a failure to disclose its chemical identity; *J. Pharmacol. Exp. Ther.* **342**, 861, 2012.)

These various approaches do not wipe out all immunological activity in the gut. Parikh notes that the movement across the gut mucosa of effector cells of the innate immune system, such as natural killers cells, can continue. "Their migration is not affected by vedolizumab," he says. Mechelen, Belgium-based Galapagos is exploring an alternative approach to disrupting leukocyte trafficking. It is testing a first-in-class, oral drug candidate, GPLG0974, which reduces neutrophil migration to the gut, by inhibition of the free fatty acid receptor 2 (FFA2). A G protein-coupled receptor involved in controlling neutrophil chemotaxis, FFA2 is upregulated in IBD. IBD is actually characterized by excessive gut infiltration of neutrophils—fecal levels of calprotectin, a protein abundantly expressed in neutrophils, is used to distinguish between IBD and non-inflammatory GI conditions. The aim, says Gerben van't Klooster, vice president of portfolio development at Galapagos, is to reduce rather than eliminate neutrophil infiltration to the gut, as the cells are the first line of defense against bacterial infection and are necessary to maintain the balance of the gut microbiome. "You don't want to have no neutrophils in the GI tract, because they're there for a reason," he says. Neutrophils can, he says, reach the gut by alternative pathways.

Modulating leukocyte migration to the gut as a means of curbing inflammation seems finally to have achieved the necessary risk-benefit balance for IBD patients. Approval of Entyvio would mark a significant milestone for many patients. "It's not the end of what may be possible," says von Andrian. "There will still be disease activity with this treatment. It's not going to be a cure for most patients."

Cormac Sheridan *Dublin*