Low-molecular-weight albumin drug touted for severe osteoarthritis

An unconventional therapy for severe knee osteoarthritis may soon be reviewed by the US Food and Drug Administration (FDA), if all goes to plan for drugmaker Ampio Pharmaceuticals. The Englewood, Colorado–based company expects to file a biologics license for its Ampion therapy by the third quarter of this year. It hopes that data from two phase 3 trials will be sufficient to convince the FDA of Ampion's efficacy in a notoriously difficult indication, for which there are no approved drug therapies.

The company reported last December that 71% of patients in a pivotal phase 3 trial responded to the therapy, according to criteria defined by two international clinical networks, Outcome Measures in Rheumatology and Osteoarthritis Research Society International. Responders had a 53% pain reduction from baseline (as measured by part A of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)), a 50% improvement over baseline in function (as measured by WOMAC C) and a 45% improvement in quality of life (as measured by patient global assessment) over baseline.

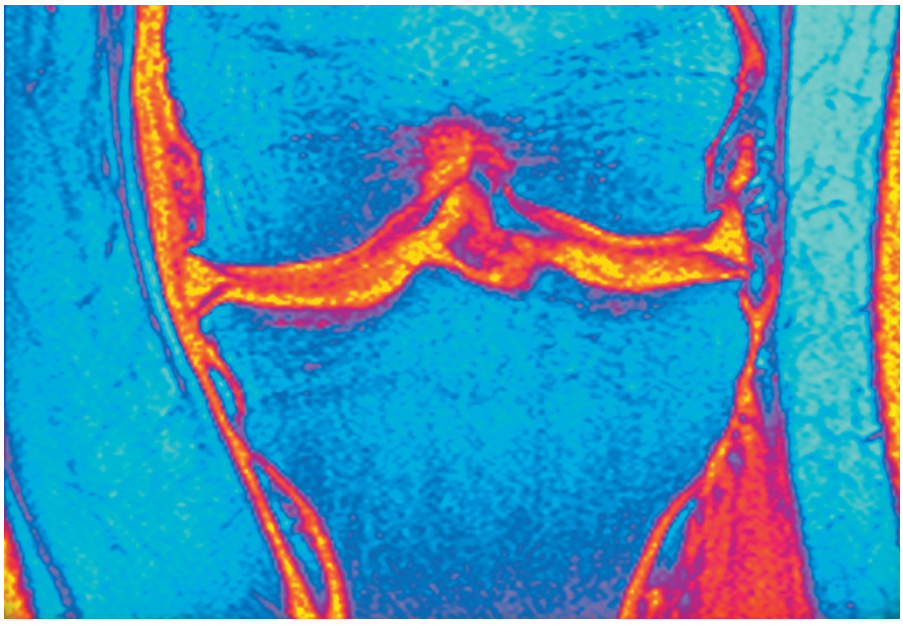
But the trial design has received criticism, particularly for its use of historical saline controls from other trials. CEO and chairman Michael Macaluso counters that the Ampion trials recruit the most severe cases, as defined on the five-point, X-ray-based Kellgren–Lawrence (0–4) scoring system. "In the last trial we did, we only took KL4s," he says. "Nobody goes after that patient population."

Ampion is a low-molecular-weight filtrate of commercial human serum albumin (HSA), which is administered directly to affected knee joints by injection. HSA, the most abundant protein in human serum, has multiple functions, including the transport of hormones, fatty acids, ions and bile salts, as well as the maintenance of osmotic pressure. It has a long history of use in restoring blood volume in trauma and surgery patients. Ampio's CSO and founder David Bar-Or has published widely on Ampion and its underlying mechanism. He has attributed its effects to various mechanisms, including the development of a microenvironment in the knee that is "conducive to stem cell infiltration, maintenance, and differentiation" (*Stem Cells Transl. Med.* **4**, 945–955, 2015). Other proposed mechanisms include an increase in anti-inflammatory prostaglandin signaling via upregulation of cyclooxygenase 2 (*Biochem. Biophys. Rep.* **8**, 68–74, 2016), and the action of aspartyl-alanyl-diketopiperazine, a fragment derived from HSA, in reducing inflammatory cytokine production by T cells (*J. Trauma* **64**, 35–41, 2008).

Osteoarthritis is characterized by the progressive degeneration of cartilage in the affected joint, which has little or no inherent capacity for repair. Pain and disability are the most common symptoms, and current treatment options are limited to opioids, hyaluronic acid or corticosteroids—or to a risky and costly joint replacement procedure, total knee arthroplasty. The company is positioning Ampion as providing relief for signs and symptoms of osteoarthritis of the knee but has also claimed it has disease-modifying potential. "The clinical endpoints they are looking at are patient-reported responses. To suggest that this is truly a disease-modifying treatment would require structural assessment of the joint," says Frank Barry, professor of cellular therapy at the National University of Ireland, Galway. "It seems as if it's a pain relief treatment."

The company, which is quoted on the NYSE American exchange in New York, is currently in breach of its listing requirements, because of insufficient stockholder's equity, but it is actively seeking either a license or an acquisition deal. Talks with 14 interested parties are underway, Ampion's Macaluso says. "There's such a large appetite for anything that represents a therapeutic opportunity for osteoarthritis. I would expect pharmaceutical and medical device companies would be all over them if they have a credible story to tell," Barry says.

Cormac Sheridan *Dublin*



Living Art Enterprises, LLC/Science Source

The progressive cartilage damage in osteoarthritis is irreversible and no treatments exist to attenuate the damage.

"We have a lot of finger-pointing that ignores shared complicity for pricing practices that are eroding trust in both payors and innovators. I hope that you'll act before that trust is eroded completely." FDA Commissioner Scott Gottlieb gives biosimilars' pricing as an example of a faulty system, during a conference of healthcare professionals, wading into a discussion from which the agency has historically shied away. (*STAT*, 7 March 2018)

"[GSK CEO] Walmsley wants the company to focus on 'real winners'—medicines that generate substantial returns. She's correct in her assessment that GSK would have had trouble making money on gene therapy for MLD [metachromatic leukodystrophy]." Maria Kefalas, mother to a child with MLD, bemoans GSK's decision to divest the company of its gene therapy assets for several monogenic diseases. (*STAT*, 8 March 2018)

"Under Trump, this is the one flickering chance of getting it changed. This is the one chance to make a broad impact." Cassie Edgar, from law firm McKee, Voorhees & Sease, who chairs BIO's committee on animal biotech policy, refers to a push from animal biotech lobbyists to move genetically engineered animals' oversight from the FDA, that demands years of safety testing, to the USDA, whose stance is that gene edited plants are not genetically modified. (*MIT Technology Review*, 12 March 2018)