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Orthopedics This Week

Could This Be Orthopedics' Future?

By Robin Young

What if steroid pain relief lasted months instead of weeks? Or what if an inhibitor of TrkA, a pathway known to have the largest pain relief signal ever seen in osteoarthritis, was injected intra-articularly with little or no systemic effect?

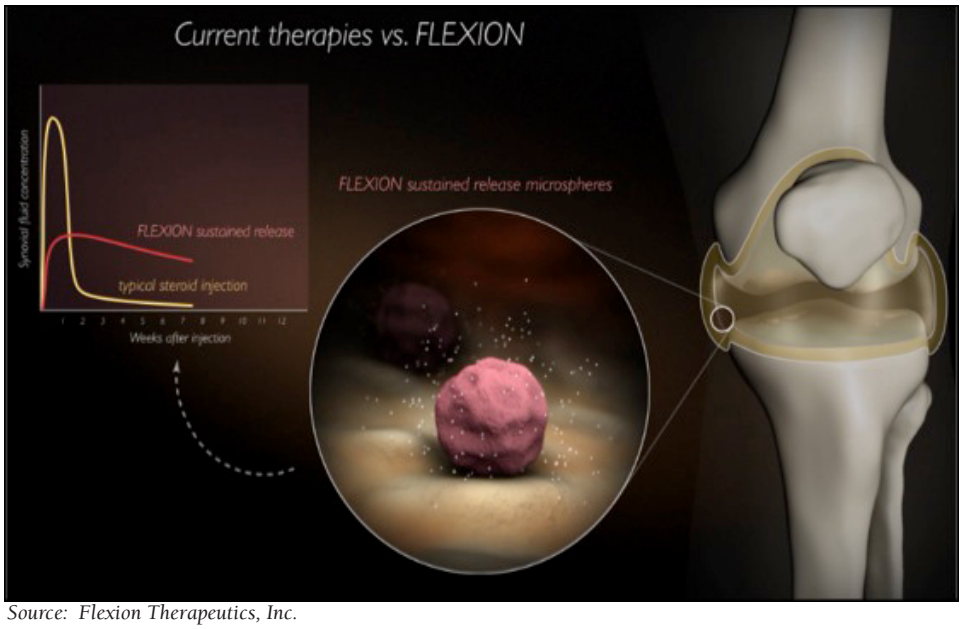
Finally, what if these injections modified the disease of osteoarthritis?

There's a Boston-based company named Flexion Therapeutics, Inc. whose products could well extend steroid effectiveness dramatically, bring other novel therapies to the physician office and deliver new levels of pain relief to patients suffering from osteoarthritis. The products, which have yet to be properly branded, are:

1. FX005 – an anti-inflammatory, sustained release, intra-articular injection for patients with osteoarthritis (second-line treatment)
2. FX006 – a first-line sustained release, intra-articular steroid injection for pain associated with osteoarthritis
3. FX007 – a non-narcotic analgesic, sustained release, intra-articular injection for pain associated with end-stage osteoarthritis and for patients who are headed for joint reconstruction surgery.

By licensing therapies from AstraZeneca and Merck and then combining them with known and FDA-approved sustained release formulations, Flexion appears to be well on its way to bringing to market three novel, longer lasting and more effective intra-articular treatments for pain associated with osteoarthritis.

If these compounds successfully make it through the FDA gauntlet, they could change current care patterns by delaying joint recon surgeries and increasing care incidence at such front line care centers as the physician office or pain clinic.



Source: Flexion Therapeutics, Inc.

Just before the American Academy of Orthopaedic Surgeons (AAOS) annual meeting, *OTW* sat down with Flexion CEO Michael Clayman to learn more about these compounds and his company's progress.

OTW: It's been two years since Flexion acquired FX005 and FX007 from Astra Zeneca and originated FX006 itself. Can you describe these anti-inflammatory and other compounds and which orthopedic indications they address?

Michael Clayman: To frame this discussion, since we acquired those compounds we decided to focus on the intra-articular treatment of osteoarthritis and we added a new sustained release product.

We are attracted to the osteoarthritis space due to the enormous size of the unmet medical need. There are well over 100 million people worldwide with symptomatic osteoarthritis with approximately 27 million in the United States. Available pain relief therapies for joint osteoarthritis are, to put it diplomatically, imperfect. Oral therapies have modest efficacy and have black box warnings for organ toxicity. Intra articular injections consist of steroids and hyaluronic acid. Steroids actually work quite well in terms of pain relief but last only a couple of weeks on average and hyaluronic acids, while very popular, hardly separate from placebo in controlled clinical trials.

We embraced a sustained release approach to intra-articular therapies which we expect will deliver persistent therapeutic concentrations of drug in joint for months and yet with vanishingly low systemic concentra-

CEO Michael Clayman/Source: Flexion Therapeutics, Inc.

tions which should provide desirable safety profiles.

Our first product, the one that is in clinical study now, FX005, is a p38 Mitogen-Activated Protein (MAP) kinase inhibitor. The p38 target is an enzyme that plays an important role in the inflammatory cascade. It also plays an important role in processing pain signals.

So p38 is an attractive target at two levels (mediating the inflammatory cascade and processing pain signals). In the past, industry developed p38 inhibitors that were given systemically. The problem was that systemic use of p38 inhibitors was associated with unacceptable toxicities despite the fact that it demonstrated anti-inflammatory and pain relief effects. We think a sustained release, intra-articular approach might afford physicians the opportunity to give a p38 inhibitor its best chance to work locally while avoiding those systemic toxicities.

OTW: Mike, that particular p38 inhibitor, is that the one you're thinking about as a second-line therapy for joint pain associated with osteoarthritis?

Michael Clayman: Correct. It is the first that we've placed into clinical development and we expect it to be used for those patients who have advanced to needing something beyond the intra-articular steroids.

Of course, one of the other two products we have in the pipeline is FX006, a sustained release steroid. As I mentioned, while steroids work quite well in terms of pain relief because they are out of the joint in a matter of days they don't deliver persistent pain relief. The pain relief they do deliver wanes, on average, in about two weeks. We think that our sustained release steroid has the opportunity to prolong that benefit out to three months or more. It would be positioned more toward front line therapy.

We expect that we will be in clinical development with our steroid product this year. The initial study will be a Phase 2b dose ranging study comparing three different doses of our sustained release steroid intra-articularly to the very commonly prescribed immediate release intra-articular steroid, Kenalog. The study would be powered to demonstrate superiority to Kenalog at time points beyond two weeks in terms of pain relief.

The third product we have in the pipeline is FX007, a TrkA antagonist. TrkA is the receptor for nerve frowth factor (NGF). We know that the nerve growth factor/TrkA pathway is an important one for mediating pain because Pfizer, for example, and other companies have developed monoclonal antibodies to NGF and when administered systemically in clinical studies, you see the largest pain relief signal ever seen in osteoarthritis.

The problem with systemically administered anti-NGF monoclonal antibodies is that they are associated, in a small percent of patients, with accelerated progression to joint replacement. As a result, the FDA put all the anti-NGF programs targeting osteoarthritis on clinical hold.

So why would we be interested in interrupting a pathway which has this potential cloud over it?

Three reasons:

1. **We're local.** With the sustained release format we would expect no meaningful systemic exposure and thereby avoid any systemic adverse events associated with the anti-NGF.
2. **We're intermittent** as opposed to the anti-NGFs which were administered every 60 days for up to two years. That approach essentially created a 100% blockade of NGF. By contrast we would be giving our drug intermittently every several months to allow the drug to ultimately come off the receptor.
3. **We're focused on end-stage patients.** These are patients who've progressed to the point of needing knee replacement. These are patients who have crossed the pain threshold and there is nothing that is really helping them adequately in terms of pain relief except knee replacement. We would offer this therapy as a way of addressing their pain while they wait for the surgical intervention. By focusing on that

end-stage knee patient population we would hope to limit the potential regulatory concerns about accelerated progression to joint replacement because we would be treating a joint that was already on the path to replacement.

OTW: Do you have a good guess as to why anti-NGF would accelerate the path to joint replacement?

Michael Clayman: There are two dominant theories:

1. By so effectively relieving pain you've created the conditions for over-use of the affected joint. An osteoarthritic joint which would otherwise have provided pain feedback signals is now rendered almost pain free. And the patient does things with that joint that they wouldn't normally have been able to do.
2. The other theory is that there is a systemic effect associated with blocking NGF. NGF has trophic effects. It may be involved importantly in neuro-vascular remodeling. One clue that this might be the case comes from anti-NGF clinical trials where patients who enter with index knee pain, leave the trial with a shoulder replacement.

OTW: Let's go to the regulatory question—it's seems to us that your first compound, FX005, the intra-articular, sustained release p38 MAP kinase inhibitor, is furthest along to commercialization.

Michael Clayman: While it is the first product that we've advanced to clinical development, we think the path to commercialization may actually be faster with FX006, our sustained release steroid. That's because FX006 may qualify for so called 505(b)(2) status since it represents a new formulation of an already approved drug, triamcinolone acetonide. Because the p38 inhibitor in FX005 is a new chemical entity it will likely require more extensive clinical testing.

But as it relates to FX005, the proof of concept study, which followed a single ascending dose study, will deliver its data in the second quarter of this year. A total of 140 patients will have been assessed. Assuming we have a positive signal in terms of clinically meaningful pain relief we will progress that compound to Phase 2b dose ranging.

These studies are powered to demonstrate a magnitude of pain relief substantially in excess of that shown with hyaluronic acid in controlled clinical trials. So, assuming the study is positive, we should have a pretty encouraging pain relief signal and we would advance it to Phase 2b dose ranging and then Phase 3.

OTW: FX005, is it being compared against hyaluronic acid?

Michael Clayman: Actually, in our initial trials of FX005 we're comparing it to placebo but we're looking for a magnitude of pain relief that would be two to three times that seen with hyaluronic acid. We are considering comparing it head-to-head with hyaluronic acid at the right time.

OTW: Any evidence that these compounds might be disease modifying?

Michael Clayman: We believe that both the p38 inhibitor (FX005) and the sustained release steroid (FX006) have the potential to be disease modifying. There's actually a substantial amount of pre-clinical data that suggest that blocking the p38 pathway would translate into a disease modifying effect. And increasingly there is a clinical view that synovitis is an important driver to joint destruction. So, quelling synovitis for a prolonged period of time has the potential to be disease modifying.

An NIH [National Institutes of Health] grant was awarded recently to look at exactly that question as it relates to immediate release steroids. The grant funds a clinical study in which clinical investigators will give immediate release steroids every three months for two years with imaging evaluations along the way. If that approach shows any beneficial effect it would be quite logical that a sustained release steroid might actually improve on that.

So I think the scientific view is leaning increasingly toward the potential of steroids, delivered in the proper way, having disease modifying potential.

OTW: Is it your plan to go for an indication for osteoarthritis in any joint—regardless of whether it is knee, hip, shoulder or facet?

Michael Clayman: Our clinical development programs are aimed at osteoarthritis of the knee, which is the most commonly injected joint. We anticipate that in time we will also be doing clinical studies of other joints.

OTW: Thank you very much Michael. These are very interesting products and best of luck. ♦

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