



ACTIVE IMPLANTS:

To Boldly Go Where Orthopedics Devices Have Rarely Tread

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Active Implants' NUsurface Meniscus Implant is on an FDA regulatory pathway that is rarely traveled by orthopedics devices. It is pursuing a de novo classification and it has one of only two-ever Breakthrough Device designations given out to date by the FDA's Orthopedic Branch.

One of the most problematic unmet clinical needs in orthopedics is knee pain. This is especially true for patients with damaged or deteriorating menisci who are too young for a knee replacement but continue to have debilitating pain following pain management therapy, physical therapy, injections, repair techniques, or meniscectomy. Between 700,000 and 1 million arthroscopic partial meniscectomies are performed annually in the US in an attempt to alleviate knee pain and allow patients to maintain or return to an active lifestyle. For younger patients, surgeons can try to repair the tear or replace the meniscus with an allograft implant. However, for a growing number of middle-aged patients, options are limited. Recent studies show that many patients in the 40-60 age group continue to experience persistent, quality-of-life-impacting pain following meniscectomy.

Memphis, TN-based **Active Implants LLC** plans to be the first to offer a much-needed device solution for this under-served and rapidly increasing US patient population. The company, founded in 2004, is on an FDA regulatory path that is rare in orthopedics. This September, its *NUsurface* Meniscus Implant received the second-ever Breakthrough Device designation given out by the FDA's Orthopedic Branch along with establishing a *de novo* review pathway. Informally referred to as a *de novo* 510(k), the review pathway is reserved for novel, low-to-moderate-risk devices that are not substantially equivalent to already marketed devices.

The *NUsurface* Meniscus Implant is intended as a cost-effective, bridge procedure for patients 40 to 60 years of age with persistent knee pain following medial meniscus surgery. The device is implanted using a proprietary set of instruments through a small incision. The procedure may be performed in an outpatient setting, and is reversible. *NUsurface*, available in six sizes, is composed of a polyethylene-reinforced polycarbonate urethane that mimics the function of the natural meniscus (see *Figure 1*). It serves to redistribute loads transmitted across the knee joint without requiring fixation to bone or soft tissues.

Following its CE mark approval in 2008, Active Implants embarked on a post-market multicenter trial, and subsequently refined the device design, surgical technique and targeted patient population, as it prepared to initiate on its US regulatory path. The company launched its US clinical efforts in 2014. Following the FDA's release of guidance on the then-new direct *de novo* pathway (where no prior 510(k) submission and rejection is required), and numerous filings, Active Implants mapped out a *de novo* pathway for its device. This past July, it completed enrollment in two concurrent pivotal trials to evaluate the safety, effectiveness, and superiority of its *NUsurface* Meniscus Implant in support of its FDA clearance. It is targeting an entrance into the US market in the first half of 2021.

"In other segments like ophthalmology and cardiovascular, there have been many additional *de novo* 510(k)'s cleared. For orthopedics, this is fairly unique and new," says Ted Davis, Active Implants' President and CEO, in a recent interview with *Market Pathways*. Davis, who began his career as a biomedical engineer, joined Active Implants in January 2017, with more than 25 years of experience in the life sciences

Figure 1



NUSURFACE MENISCUS IMPLANT



NUSURFACE MIMICS THE FUNCTION OF THE NATURAL MENISCUS

Source: Active Implants

industry as an investor and senior executive. Previously, he served as CEO of MicroPort Orthopedics, and president of its predecessor Wright Medical Technology's global OrthoRecon division from 2012 through 2015. Prior to joining Wright in 2006, Davis spent 10 years in the life sciences venture capital field, serving on the boards of multiple biotechnology and medical device companies while at MB Venture Partners and Vector Fund Management.

"Whenever you're bringing something to market that's a transformational therapy, you're living a bit more like in the traditional cardiovascular environment or even the drug environment, where you have to be able to enroll robust clinical trials, have excellent data collection, and good oversight of those sites. I think that in orthopedics that's a muscle, if you will, that is not as well developed as other specialties," says Adam Klyce, Active Implants' VP of Marketing and Clinical Operations, in a recent interview with *Market Pathways*. Prior to joining the company in 2015, Klyce was vice president of marketing at spinal implant company Spartek Medical Inc., and prior to this, director of marketing at St. Francis Medical Technologies.

A Rare Orthopedic Breakthrough Designation

This September, Active Implants received the news that the *NUsurface* Meniscus Implant, with its focus on a specific high-need patient population who have tried surgery and failed, was granted a Breakthrough Device designation from the FDA. In Davis' view, this rare orthopedic designation is significant for the company's FDA regulatory journey in two ways.

First, it ensures ongoing dialogue with FDA in preparing all the filings for the *de novo* application. "If we have questions, we can have sprint discussions with the FDA to answer very specific questions. You set up a normal meeting cadence [with the agency], so that you get a clear perspective. Instead of filing and finding out they have five more questions, hopefully we are able to determine any questions they have and get those in our initial filing. Secondly, they have a more complete file to evaluate, and hopefully that truncates the review time on the back end," says Davis.

Enacted in 2017 as part of the 21st Century Cures Act, the FDA's Breakthrough Devices Program provides an expedited development and review path for medical devices to be cleared for sale in the US. The program, launched in 2015 as the Expedited Access Pathway, focuses on devices for irreversible or debilitating, as well as life-threatening conditions. If granted the designation, a device will also receive prioritized review on future regulatory submissions, including Q-Submissions, Investigational Device Exemption (IDE) applications, and marketing submissions, according to FDA. To date, approximately 200 devices have been granted the Breakthrough Device designation.

A Merging of Two Trials

Active Implants is fortunate in that it was able to work with the FDA through the Pre-Submission process to combine data from its two concurrent studies into one data set, called the MERCURY study group. “We had several Pre-Sub interfaces with FDA over the last couple of years. It’s unique in that we had two different clinical studies that we were enrolling and, through the Pre-Sub process, we worked with the FDA and with their collaboration, we combined the data into one data set,” says Davis. “They’ve been very responsive, and I think that’s what sets us up well for our Breakthrough designation.”

The company’s two trials enrolled a combined 243 patients, 176 of whom received the *NUsurface* Meniscus Implant. One of these, the Verification of the Effectiveness of the *NUsurface* System (VENUS) trial, is a randomized, multi-centered, prospective, controlled study to demonstrate superiority of the *NUsurface* meniscus implant compared to the current standard-of-care for patients with persistent knee pain following meniscectomy surgery. VENUS enrolled 128 patients at 10 US study sites. This study took place before a direct *de novo* pathway existed with the FDA. The other, the Safety Using *NUsurface* (SUN) trial, is a single-arm study that is assessing the safety and probable benefit of the *NUsurface* Meniscus Implant in restoring function similar to that of a natural, healthy meniscus. It enrolled 115 patients at 13 US study sites.

Active Implants conducted the two different types of studies concurrently in order to bring the *NUsurface* Meniscus Implant to market as quickly as possible. “The FDA was very collaborative with us to help us find the best pathway for this device. We worked hard to make sure that we were enrolling the same patient populations, even though they were two different trial designs,” says Klyce.

“Superiority data adds an additional level of confidence from our standpoint and to surgeons’ standpoint as to that we’re not just offering something that is equivalent to something else, but we’re offering something that is hopefully yielding data that would show we are indeed offering a superior result,” says Erik Harris, Active Implants’ VP of Global Market Access, Health Economics and Reimbursement, in a recent interview with *Market Pathways*. Harris, who joined Active Implants in 2017 following senior positions in global reimbursement and market access at Wright Medical Technology, BioMimetic Therapeutics, and Zimmer, has 27 years of experience in areas including market access, reimbursement and health economics, healthcare policy, provider/payor relations, and legislative and government affairs.

The combined two-year trial results, clinical observations and other data will be included in Active Implants’ *de novo* application to the FDA. “In June of 2020, we’ll have the last patient at the two-year endpoint, so we’re coming up on that next regulatory milestone with the FDA,” says Davis. As part

of the Breakthrough process, the company is engaging with its FDA review group regarding its clinical data every month.

What’s more, this data will be critical for the US reimbursement piece of the puzzle, as described below. “Clinical work is going to become more and more of what’s required of new and differentiated technologies for both regulatory and reimbursement needs,” Davis tells *Market Pathways*.

Filling a Treatment Gap

This patient selection challenge brings up an important issue that Active Implants faces with its new and differentiated meniscus implant technology. “While we enrolled patients ranging from 30 to 69 years of age, the average was around 50. There aren’t really any other implants available for this middle-aged patient group besides a uni-compartmental knee replacement, and the average age of the patients in the studies used to approve those range from 60 to 65,” says Klyce. “But now, they’re being used in younger and younger patient populations. When you try to compare what we’re doing to what’s been published for those devices, everything from device longevity, complications, adverse events, and clinical outcomes, they all need to be calibrated to a younger patient population,” he continues.

Importantly, knee replacements placed in younger populations will most likely require future revision surgery, which is more complex and costly. With no comparable populations, Active Implants’ control group is non-operative care, as that’s what is used in the 40+ age group once partial meniscectomy or repair attempts have failed.

“If we’re successful in getting FDA clearance and the [*NUsurface*] product is a commercial success, then it’ll be the first, and maybe only, orthopedic implant aimed at this population,” adds Klyce.

Outside the US, Active Implants initiated a limited commercial release in Belgium, Germany, Italy, and Israel, in just the last few months, and is looking to enter the United Kingdom next year. The company has European offices in Haarlem, The Netherlands, and R&D facilities in Netanya, Israel. Its implant is manufactured in Israel, although the company says it is planning on “scaling up a US manufacturing vendor” to complement that production. The device has been placed in more than 350 patients worldwide to date.

In Europe, there’s a lot of unmet need for meniscus products like *NUsurface*, and there is broad physician acceptance, Klyce tells *Market Pathways*. However, the company is rolling its product out in a controlled manner. “A challenge is that you’re going to have people being pressured to try this in patients who don’t have other good options. But, maybe for them this isn’t the ideal treatment. It will be a challenge to control the indications for use and make sure our customers are selecting good patients at the

beginning ... we're setting up what we think will be a model for how we will sell the product here in the US."

Reimbursement and Market Access

In terms of reimbursement outside the US, Active Implants is addressing its strategy market by market for the four countries in which it has launched to date—especially in light of austerity measures taken in recent years, says Davis. "We've been able to assess each market before we enter it. We know exactly what we need to execute to. We know what the timeline is, and then ultimately what we think we'll get paid for the device."

In the US, the company's reimbursement strategy is based on the power of its clinical superiority and randomized controlled data, because, as Davis describes it, "that's what the large insurance companies are looking for in today's day and age from a new technology. You have to work very effectively with AMA [the American Medical Association] in obtaining the right coding for your products." And, with its Breakthrough designation, Active Implants has already demonstrated that its technology is new and has a clinically significant improvement over existing technologies.

Active Implants is assessing multiple coding options for the US market. It is working toward either establishing new coding or modifying existing codes through the support of specialty societies, or using potential coding options available via the Centers for Medicare & Medicaid Services' alternative Medicare payment pathways. The company is engaging with academic specialty societies such as the Arthroscopy Association of North America (AANA) and the American Orthopaedic Society for Sports Medicine (AOSSM) on coding initiatives for reimbursement of *NUsurface*.

The *NUsurface* implant is also a very cost-effective option, says Klyce. "We feel pretty good ... when you compare the two- or three-year costs of our therapy compared to the cost of a patient's first partial knee replacement. Or even just continuing conservative treatment for those two to three years. Our cost is about the same as conservative treatment but also it's delivering them much better pain reduction and physical function improvement ... and we're less expensive than arthroplasty."

"The parties that actually purchase the device are the facilities, whether that is an inpatient hospital, the outpatient hospital setting, or a freestanding surgery center. Those facilities have a lot of interest in understanding what is this going to mean to them in terms of their profit margin opportunity, which relates to the coding and the payment model," says Harris. "There is maybe also some strategic market positioning that facilities might be able to look to. Success in market access is how can you demonstrate the value of your product, the procedure, to the various parties involved."

And, payors want to know what the value of a new service is compared to what they may already be covering for other

procedures in the need continuum, says Harris. "As *NUsurface* is a new product, there are no coverage policies, so part of the process is helping payors understand and become educated on the full economic value of what *NUsurface* offers to patients that they would be paying claims for," he explains. "There's also the value that a product provides that is resolving patient pain and getting them back to normal activities. They are already paying for interventions for this group of patients. Transparency with peer-reviewed clinical data results, adverse events, and other elements are critical in this process, so that payors understand the clinical value of what you are bringing to the healthcare system," says Harris. He also advises companies that are working on their coding strategy to do a comprehensive coding assessment.

"Our real challenge with reimbursement is just the same one that any innovative technology has, which is there's no predicate established for it already, and you have to create a place and you have to do that after you get FDA approval usually, which is when you have the financial pressure of selling, but no code," says Klyce.

Advice from the Trenches

With more than 11 years of clinical, development, and regulatory work behind the *NUsurface* device so far, Active Implants management offered some lessons learned to date. For Klyce, these include focus, organization, and open communication.

"You have to be really focused on building the right clinical infrastructure, meaning your support team to support the sites, and help them through all the processes. And, you've got to have the right information technology and data capture platforms to make it easier on the back end to do your analytics," he says.

Building on all that, it's important to maintain a dialogue with FDA, especially as there have been changes in the *de novo* program. "You have to maintain open dialogue with the agency, so that when you have questions, when you have aspects that you want to make sure you're doing right, you get their feedback," Klyce adds.

And, for device companies that are developing their market access strategy, payors are going to be probably the most important group of stakeholders because they hold the ultimate purse strings, advises Harris. "Are they going to cover a procedure, and what are they going to pay for that procedure?"

Harris also recommends that companies partner with a vendor that is able to coordinate payor medical director insight panels, "so that you can get some early feedback on your progress and what they would suggest as ways to fill gaps in your overall market access strategy by the time that you bring the product to market." Via these panels, companies are able to obtain valuable double-blinded, qualitative feedback from payors. 