

## LUMBAR DEGENERATIVE DISEASE

### Background:

It is estimated that 60% to 80% of the adult population will experience low back pain at some time in their lives with up to 5% experiencing this pain on a yearly basis. Chronic low back pain is one of the most common reasons for physician visits in the United States, is among the leading causes of employee absenteeism and disability, and accounts for a relatively large percentage of all U.S. healthcare expenditures.

The causes of low back pain are multifactorial and the specific pain generator typically cannot be isolated. Normal aging of the lumbar spine involves a sequence of degenerative changes that likely start on a biochemical and cellular level and ultimately manifest as the changes that are seen clinically. Each component of the three-joint complex that makes up a functional spinal motion segment (intervertebral disc, two facet joints, ligamentous structures, and vertebral bodies) undergoes changes with aging and degeneration.

While the initiating factor is rarely identified and while it is not clear how each of these degenerative processes contribute to the observed clinical picture, it is important to consider the changes that occur in each part of the spinal motion segment in designing clinical trials to study spinal devices intended to treat lumbar degenerative disease. The intervertebral disc is thought to show decreased proteoglycan water binding within the nucleus pulposus and often a loss of disc space height. It is hypothesized that as the nucleus loses water, stresses are unevenly distributed to the annulus fibrosus altering the mechanical loading characteristics. This, coupled with the shift in collagen content and distribution that is thought to occur in the annulus with aging, can lead to bulging and/or radial tears. As the degenerative process continues, the disc becomes more fibrous and disorganized until ultimately there is no clear distinction between the nucleus and the annulus. The vertebral end-plates are thought to thin and become less permeable with aging thus compromising the nutrition of the disc and impacting disc metabolism, and as degeneration progresses, osteophytes form at the end-plate-annulus junction. The facet joints are thought to settle, become more lax, and carry more load as disc height decreases as a result of degeneration. It is thought that this load transfer may contribute to accelerated facet joint degeneration. As degeneration progresses, patients may experience degenerative spondylolisthesis and/or degenerative spinal stenosis as a result of chronic disc degeneration and the resulting secondary spinal instability.

Determining a pathoanatomical diagnosis in patients with chronic low back pain is complicated by the fact that many healthy adults have abnormal findings on spinal imaging studies so that merely detecting a bulging or degenerated disc does not necessarily correlate with relevant clinical symptoms. Boden et al. looked at lumbar spine MRIs in 67 patients who had never experienced back pain or sciatica and found that in those under the age of 60, 22% had a disc herniation, 54% had a disc bulge, and 46% had disc degeneration. In patients over the age of 60, the percentages increased to 36%, 79%, and 93% respectively.<sup>1</sup> Although these degenerative processes seem to occur in the majority of people secondary to aging, it is not clear why some people become symptomatic. This is complicated by the fact that most cases of low back pain are

---

<sup>1</sup> Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects: A prospective investigation. *J Bone Joint Surg* 1990 Mar;72(3):403-8.

self-limiting in that only 7% of patients have symptoms that persist beyond 2 weeks with only 1% of those requiring prolonged treatment and even fewer eventually requiring surgical intervention<sup>2</sup>.

### **Existing Treatments:**

Because the relationship between the degenerative cascade and clinical presentation is poorly understood, it is often challenging to identify symptomatic patients who will benefit from surgical intervention. The vast majority of patients with low back pain are successfully managed nonoperatively. A wide variety of nonoperative treatments are available including physical therapy (both active and passive modalities), medications (including analgesics, anti-inflammatories, muscle relaxants, and antidepressants), patient education, chiropractic manipulation, traction, bracing, acupuncture, and injections (both epidural and facet injections). Considerable variability in treatment protocols exist based, in part, on the training of the clinician. Nonoperative conservative care has traditionally been the treatment of choice for the early stages of low back pain given that a high percentage of patients will recover with this management. If, however, symptoms persist and/or progress despite nonoperative management (particularly to the point of significantly impacting quality of life and the ability of the patient to function), surgery becomes an option. Historically, the surgical standard of care for most of these patients has been some form of spinal fusion with or without a decompressive procedure (such as laminectomy) and with or without instrumentation. Over time, less invasive discectomy procedures have been developed to treat disc herniation and more minimally invasive approaches for laminectomy and spinal fusion have evolved. In addition, total disc replacement has become an attractive option in the hope that a replacement can preserve motion, potentially improve clinical outcomes and hopefully preserve adjacent spinal motion segments. Total disc replacement, laminectomy and fusion are seen as relatively invasive procedures with significant potential for associated adverse events and complications.

### **Devices Intended to Treat Mild to Moderate Lumbar Degenerative Disease:**

Currently there is somewhat of a void between nonoperative treatment options and more invasive options such as total disc replacement, laminectomy, or fusion with few minimally invasive procedures available for earlier stage disease. As a result, recently orthopaedic manufacturers have been submitting applications for devices that are intended to treat mild to moderate lumbar degenerative disease. Per the current “standard of care”, these devices are proposed for patients who traditionally would have been treated with nonoperative, conservative care. In other words, their symptoms are seen as milder than those that would typically necessitate a disc replacement or a fusion. However, these patients are still considered sufferers of chronic low back pain in that they have failed some form of nonoperative treatment.

In general, these devices are all intended to stabilize the affected functional spinal unit, while maintaining some motion at the operative level. However, these devices are quite variable in design, function and region of implantation. Some consist of a spacer that is implanted between adjacent spinous processes theoretically designed to limit extension and/or flexion to some degree. Others are intended to fill the void created by the removal of the disc nucleus with rigid implants or injectable polymers. Still others affix to the posterior spine via pedicle screws, which are attached to some form of flexible vertical connection/member or semi-constrained articulation.

---

<sup>2</sup> Report of the Quebec Task Force on Spinal Disorders. Scientific approach to the assessment and management of activity-related spinal disorders. A monograph for clinicians. *Spine* 1987 Sep;12 (7 Suppl):S1-59.

These new devices generally involve less invasive procedures than the procedures of laminectomy, spinal fusion, or disc replacement; however, they are clearly more invasive than the conservative care techniques typically used in this patient population. Sponsors state that an important feature of many of these devices/procedures is that they do not preclude or compromise future fusion or disc replacement surgeries.

**Intended Population for Study:**

These new devices intended to treat mild to moderate lumbar degenerative disease have been proposed for the study of varying indications including degenerative disc disease (DDD), lumbar spinal stenosis, degenerative spondylolisthesis, and disc herniation. Each sponsor has taken a different approach to defining their indications for use to reflect the mild to moderately affected patient population that they intend to study. The studies for mild to moderate DDD have proposed to define a lower baseline for back pain and functional status requirements (e.g., VAS  $\geq$  30/100, ODI  $\geq$  20 or 30/100) than have traditionally been used. These studies also have proposed radiographic confirming factors defined using criteria such as modic changes; decreased disc height; scarring/thickening of the ligamentum flavum, annulus fibrosus, or facet joint capsule; presence or absence of osteophytes; presence or absence of contained herniation; and presence or absence of facet joint degeneration. Similarly, the studies for mild to moderate lumbar spinal stenosis have proposed to define lower baseline leg pain and functional status requirements than have traditionally been used. In general, each study has proposed a prior course of nonoperative treatment ranging in length from six weeks to six months.

In contrast, FDA has typically recommended that patients be non-respondent to a minimum of six months of nonoperative care in order to be considered an appropriate candidate for a surgical intervention for lumbar degenerative disease. FDA also prefers that baseline scores be  $\geq$  40/100 for VAS and ODI (although ODI  $\geq$  30/100 has been accepted for some disc replacement studies) in order to define a patient population of appropriate surgical candidates. For reference, traditionally FDA has recommended defining lumbar DDD for spinal IDE studies as back and/or radicular pain with degeneration of the disc as confirmed by patient history, physical examination, and radiographic studies with one or more of the following factors (as measured radiographically, either by CT, MRI, plain film, myelography, discography, etc.): instability as defined by  $\geq$  3mm translation or  $\geq$  5° angulation; osteophyte formation of facet joints or vertebral endplates; decreased disc height, on average by  $>$  2mm, but dependent upon the spinal level; scarring/thickening of ligamentum flavum, annulus fibrosus, or facet joint capsule; herniated nucleus pulposus; facet joint degeneration/changes; and/or vacuum phenomenon. A PMA-approved total disc replacement device, the Charité Artificial Disc Replacement, is indicated for "...spinal arthroplasty in skeletally mature patients with degenerative disc disease (DDD) at one level from L4 to S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. These DDD patients should have no more than 3mm of spondylolisthesis at the involved level. Patients receiving the Charité Artificial Disc should have failed at least six months of conservative treatment prior to implantation of the Charité Artificial Disc."

**Control Populations for Study:**

Several proposed studies of these new devices intended to treat mild to moderate lumbar degenerative disease have proposed nonoperative, conservative care as their study control population. These control arms are designed to include various combinations of medications,

physical therapy, patient education, and injections (epidural and facet). In addition, some proposals have considered “crossover” or “rescue” procedure designs where subjects in the control group who meet certain, prespecified criteria can be considered to receive the investigational device or a “rescue” procedure such as a fusion or total disc replacement during the course of the clinical trial.

### **Discussion of FDA Issues and Concerns Related to Clinical Trials for These Devices:**

The current standard of care for treating lumbar degenerative disease has been to surgically intervene after a reasonable course of nonoperative care has failed. In general, the objective of these new devices intended to treat mild to moderate disease is to surgically intervene at an earlier time point in the course of the lumbar degenerative process. Given the benign natural history of most cases of low back pain and the fact that most patients do not require surgical treatment, FDA is concerned that many patients suffering from more mild to moderate disease may not be appropriate surgical candidates who warrant treatment with a permanent spinal implant. Introducing additional surgical procedures and devices earlier in the lumbar degenerative disease treatment continuum could offer patients less invasive procedures that may delay the need for fusion or disc replacement, while improving pain and quality of life. On the other hand, the associated risks may not be appropriate for patients with mild to moderate disease and the benefits may not last long enough to have warranted the intervention. FDA is concerned with the challenge of determining when it is appropriate to study a surgical intervention as well as the challenge of adequately defining the patient population for whom these types of devices may be appropriate to study.

In order for a trial to yield clinically meaningful data, an adequate control group must be established. With regard to these devices intended to treat mild to moderate lumbar degenerative disease, the selection of an appropriate control group is challenging given that there does not appear to be an established surgical standard of care for those patients yet comparing a surgical investigational treatment to a nonoperative control group raises a number of issues. FDA is concerned that if a patient has truly “failed” conservative, nonoperative care, then it may not be appropriate to randomize that patient to receive further conservative care in part because doing so may introduce significant biases into the clinical trial and randomizing patients to the same treatments they have previously “failed” will likely result in extremely low success rates in the control group. On the other hand, if patients are not allowed to truly “fail” conservative care prior to randomization, any outcomes observed during the clinical trial may not be attributable to the device given the natural history of lumbar degenerative disease and the number of patients who would have recovered without any surgical intervention. In addition, it might not be ethical or appropriate to treat patients with mild disease with a permanently implanted device particularly if they have not been given an adequate trial of nonoperative care (which we realize may be challenging to define). Also in general, comparing a surgical intervention to nonoperative care introduces a potentially significant bias due to placebo effects. Conversely, due to the nature of early stage degenerative disease; these patients do not necessarily meet the criteria established for laminectomy, spinal fusion or disc replacement. If that is the case, it is not appropriate to randomize them to a laminectomy, spinal fusion or total disc replacement control group that they are not indicated for. In addition, regarding the “crossover” and “rescue” procedure designs that have been proposed, we are concerned about the potential investigator bias, patient selection bias, and patient bias that could affect which patients receive the “crossover” or “rescue” interventions and therefore could affect the clinical outcome.

A number of pain and function assessments (e.g., VAS, ODI) have become commonly accepted as surrogate endpoints for the evaluation of the status of lumbar degenerative disease in clinical trials of investigational spinal devices. FDA is concerned that these traditional spinal study endpoints may not be the most appropriate endpoints to evaluate the status of lumbar degenerative disease in subjects who have mild to moderate disease at baseline. We are also concerned that subjects with more mild disease at baseline (e.g., ODI and/or VAS of 30/100), may not achieve enough of a change on the ODI and/or VAS assessment scales to demonstrate clinically meaningful improvements to show device effectiveness and that attempts to show a faster clinical response may fail to demonstrate whether the response is durable. For example, if

a patient with mild to moderate low back pain receives a device and experiences a significant decrease in pain and is able to return to work, then he or she may be categorized as a success. However, if the patient's pain returns to baseline or worsens two to three years post-operatively, it is not clear that the patient should be considered a success. Similarly, demonstrating increased time to fusion or subsequent treatment may be useful; however, it is not clear what amount of time should be considered clinically significant.

### Questions:

1. Considering the natural history of lumbar degenerative disease, please discuss the appropriate time to intervene with a permanently implanted device intended to treat mild to moderate disease as well as the characteristics that should be used to define patients who are appropriate candidates for earlier surgical intervention. At a minimum, please consider the amount and type of conservative, nonoperative care a patient should receive and specific baseline criteria (e.g., ODI, VAS, neurologic findings, radiographic criteria) that patients should meet prior to inclusion in a spinal device clinical trial for each type of device (i.e., interspinous process spacers, nucleus replacements, pedicle screw-based systems).
2. Based on the population of appropriate surgical candidates discussed in Question #1, please discuss the most appropriate control device/procedure/therapy, operative or nonoperative, for each of these device types (i.e., interspinous process spacers, nucleus replacements, pedicle screw-based systems) intended to treat mild to moderate lumbar degenerative disease. Please consider that a clinical study must be designed to demonstrate a treatment effect. For example, it must be designed to show that any observed clinical outcome is due to the device rather than other confounding factors and treatments. Please keep in mind that in order to warrant surgical intervention for lumbar degenerative disease, it is believed that a patient should have “failed” an adequate amount of conservative therapy; however, on the other hand, a patient should not be randomized to a control treatment that they have already “failed”. If a type of “crossover” or “rescue” procedure design (as discussed above) is part of the control group study design that you discuss, please comment on how subjects who have “failed” the first treatment and thus are eligible to go on to the second treatment should be defined in order to ensure consistency among investigators in selecting those patients who go on to receive further treatment.
3. Please discuss the most appropriate clinically significant endpoints to evaluate subjects with mild to moderate lumbar degenerative disease at baseline for each type of device (i.e., interspinous process spacers, nucleus replacements, pedicle screw-based systems). Traditionally, studies of spinal devices have compared some or all of the following endpoints at the 24 month timepoint: pain and function scores; quality of life assessments; radiographic evidence of fusion and/or motion; adverse events including secondary surgical procedures; and neurological assessments. Please discuss which endpoints are the most appropriate endpoints to evaluate lumbar degenerative disease status in patients with mild to moderate disease. Also, please discuss what role, if any, demonstrating a faster response as opposed to a response at the 24-month timepoint should play. If demonstrating a faster response is considered important, please discuss the length of time the response should last to consider the device a success. Considering some of the proposed potential benefits offered by these devices (e.g., faster response to the intervention thus allowing more effective rehabilitation and quicker return to work; delay or elimination of the need for future, more invasive surgery without precluding or compromising later surgery; physical benefits such as restoration of disc height and/or disc hydration; and delay or halt in the progression of the degenerative process), please discuss the role of endpoints that may evaluate the mechanism of action of a device as well as the most appropriate endpoints to determine whether early intervention alters the course of the disease. For example, please discuss whether or not sponsors should include endpoints to demonstrate restoration in disc height and disc hydration (e.g., through objective radiographic criteria).
4. Based on your answer to Question #3, please discuss what changes to traditional spinal device study designs might be appropriate given the less invasive nature of many of these devices as well as the mild to moderately affected patient population. Specifically, please

discuss whether it is appropriate to define a smaller change in pain and function scores as clinically significant given that the inclusion criterion score may be lower. Please consider that it may be more difficult to show that subjects with mild disease at baseline have achieved enough of a change on assessment tools such as the ODI or VAS to demonstrate clinically meaningful improvement to show device effectiveness (e.g., if the ODI inclusion criterion is a score of 30, then perhaps an improvement of 10 points may be considered clinically significant as opposed to the conventionally accepted 15 points). Also, please discuss whether using a delta value larger than the traditional 10% used in spinal IDE studies may be appropriate (depending on the choice of control and type of study design).