

5.3.2.1 Overview of Pivotal Study S01-01US

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Pivotal study S01-01US was a controlled, open-label (with blinded radiographic assessment), randomized, prospective, multicenter, multinational pivotal study in which patients with single level (L3-S1) degenerative lumbar spondylolisthesis (Grade 1 or 2) and spinal stenosis underwent decompression and posterolateral spinal fusion. After signing the informed consent form, and prior to the surgical procedure, patients were randomized to treatment in a 2:1 ratio to either OP-1 Putty or a control arm, in which autogenous bone graft from the iliac crest (autograft) was used.

Patients underwent standard surgical procedures for lumbar spinal posterior decompression with concomitant posterolateral intertransverse process arthrodesis using OP-1 Putty or with autograft, as determined by randomization. Patients were evaluated postoperatively at 6 weeks, and 3, 6, 9, 12, and 24 months, and annually thereafter, until the last patient achieved 2 years of follow-up. A total of 336 patients were enrolled and randomized, and 295 were treated: 208 received OP-1 Putty and 87 received autograft. The remaining 41 enrolled patients withdrew prior to study treatment.

In the pivotal study S01-01US, Overall Success was defined in the Statistical Analysis Plan (SAP) as a composite measure requiring success on each of the following components, determined at 24 months:

- Improvement of at least 20% in the ODI from baseline
- Absence of retreatment
- Absence of treatment-emergent serious adverse events (SAEs)
- Absence of a decrease in neurological status (assessing muscle strength, reflexes, sensory and straight leg raise), unless attributable to a concurrent medical condition or to the surgical procedure by a blinded Independent Neurological Reviewer.
- Radiographic success which was also a composite measure comprising all of the following:
 - o Presence of bone formation
 - o Angulation of $\leq 5^\circ$ on flexion/extension radiographs of the affected level
 - o Translational movement of < 3 mm on flexion/extension radiographs of the affected level

The primary analysis of this endpoint was a statistical test of non-inferiority of OP-1 as compared to autograft using a modified intent-to-treat population. The test failed to demonstrate non-inferiority of OP-1 to autograft, as presented to FDA in the original application for PMA #P060021. The results of the pivotal study at 24 months postsurgery for overall success and its components are summarized below. Note that the percentage of patients achieving success in the secondary endpoints related to ODI success, absence of treatment-related serious adverse events, absence of decrease in neurological status, and the components of overall radiographic success (presence of bone, extent of angulation and translation) have been calculated with all patients who were a retreatment failure subsequent to the posterolateral fusion set to failure.