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PRODISC®-L Total Disc Replacement PACKAGE INSERT

TO BE PROVIDED IN ELECTRONIC FORMAT

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Synthes Spine

IMPORTANT INFORMATION ON THE PRODISC®-L TOTAL DISC REPLACEMENT

12/05 **GPxxxx-X**

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician (or properly licensed practitioner) that has appropriate training or experience.

Device Description

The PRODISC®-L Total Disc Replacement is a weight-bearing modular implant consisting of two endplates and one polyethylene inlay. Endplates are manufactured from CoCrMo conforming to ISO 5832-12 (1996) "Implants for surgery – Metallic materials – Part 12: Wrought cobalt-chromium-molybdenum alloy" and are available in two sizes. The superior endplates are also available in two lordotic angles. The surfaces of both the inferior and superior plates are plasma sprayed with CPTI conforming to ISO/DIS 5832-2 (1999) "Implants for surgery – Metallic materials-- Part 2: Unalloyed titanium". Fixation of the PRODISC®-L to the vertebral bodies is intended to be achieved through bone ingrowth, with initial, stabilization by a large central keel and two small spikes on the surface of the two endplates. The inlays are manufactured from ultra-high molecular weight polyethylene (UHMWPE), and are available in three thicknesses with anterior-posterior and lateral sizing consistent with the endplate sizing. The inlay snap-locks into the inferior endplate and provides the inferior convex bearing surface that articulates with the concave bearing surface of the superior endplate. The range of motion allowed by the PRODISC®-L is 13° of flexion, 7° of extension, ±10° of lateral bending, and ±3° of axial rotation, as measured through *in vitro* testing.

The following tables describe the available sizes and configurations of the PRODISC®-L Total Disc Replacement components:

PRODISC®-L Endplates			
Size	Approx. Dimensions		Angles (degrees)
	A/P (mm)	Lateral (mm)	
Inferior Endplate – Medium	27	34.5	NA
Inferior Endplate – Large	30	39	NA
Superior Endplate – Medium	27	34.5	6 °
Superior Endplate – Medium	27	34.5	11 °
Superior Endplate – Large	30	39	6 °
Superior Endplate – Large	30	39	11 °

PRODISC®-L Inlays			
Size	Approx. Dimensions		Height (mm) (Assembled)
	A/P (mm)	Lateral (mm)	
PE Inlay – Medium	26	23	10
PE Inlay – Medium	26	23	12

PE Inlay – Medium	26	23	14
PE Inlay – Large	29	25	10
PE Inlay – Large	29	25	12
PE Inlay – Large	29	25	14

Indications

The PRODISC®-L Total Disc Replacement is indicated for spinal arthroplasty in skeletally mature patients with degenerative disc disease (DDD) at one level from L3-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 grade 1 spondylolisthesis at the involved level. Patients receiving the PRODISC®-L Total Disc Replacement should have failed at least six months of conservative treatment prior to implantation of the PRODISC®-L Total Disc Replacement.

Contraindications

The PRODISC®-L Total Disc Replacement should not be implanted in patients with the following conditions:

- Active systemic infection or infection localized to the site of implantation
- Osteopenia or osteoporosis defined as DEXA bone density measured T-score < -1.0
- Bony lumbar spinal stenosis
- Allergy or sensitivity to implant materials (cobalt, chromium, molybdenum, polyethylene, titanium)
- Isolated radicular compression syndromes, especially due to disc herniation
- Pars defect
- Involved vertebral endplate dimensionally smaller than 34.5 mm in the medial-lateral and/or 27 mm in the anterior-posterior directions
- Clinically compromised vertebral bodies at affected level due to current or past trauma
- Lytic spondylolisthesis or degenerative spondylolisthesis of grade > 1

Warnings

Correct placement of the device is essential to optimal performance. Use of the PRODISC®-L Total Disc Replacement should only be undertaken after the surgeon has become thoroughly knowledgeable about spinal anatomy and biomechanics; has had experience with anterior approach spinal surgeries; and has had hands-on training in the use of this device.

Precautions

To ensure correct and stable joining of the modular PRODISC®-L Total Disc Replacement components, ensure that the combination dimensions are congruent. See the surgical technique manual for step by step instructions.

To prevent damage to the bearing surfaces and ensure a solid assembly, clean each component with sterile saline before joining to ensure that blood or other debris is not trapped within the assembly.

The safety and effectiveness of this device has not been established in patients with the following conditions:

- more than one vertebral level with DDD
- prior fusion surgery at any vertebral level
- facet joint disease or degeneration
- back or leg pain of unknown etiology
- Paget's disease, osteomalacia, or other metabolic bone disease
- morbid obesity (BMI>40 or weight more than 100 lbs over ideal body weight)
- pregnancy
- taking medications known to potentially interfere with bone/soft tissue healing (e.g., steroids)
- rheumatoid arthritis or other autoimmune disease
- systemic disease including AIDS, HIV, Hepatitis
- active malignancy.

Patient selection is extremely important. In selecting patients for a total disc replacement the following factors can be of extreme importance to the success of the procedure: the patient's occupation or activity level, a condition of senility, mental illness, alcoholism, or drug abuse, and certain degenerative diseases (e.g., degenerative scoliosis or ankylosing spondylitis) that may be so advanced at the time of implantation that the expected useful life of the device is substantially decreased.

Correct selection of the appropriate implant size is extremely important to assure the placement and function of the disc. See the surgical technique manual for step by step instructions.

Surgical implants must never be re-used or re-implanted. Even though the device appears undamaged, it may have small defects and internal stress patterns that may lead to early breakage.

Use aseptic technique when removing the PRODISC®-L Total Disc Replacement components from the innermost packaging.

Use care when handling a PRODISC®-L Total Disc Replacement implant to ensure that it does not come in contact with objects that could damage the implant. Exercise care to ensure that implantation instruments do not contact the highly polished articulating surfaces of the endplates. Damaged implants are no longer functionally reliable.

In order to minimize the risk of atraumatic periprosthetic vertebral fractures, surgeons must consider all co-morbidities, past and present medications, previous treatments, etc. Upon reviewing all relevant information the surgeon must determine whether a bone density scan is prudent. A screening questionnaire for osteoporosis, SCORE (Simple Calculated Osteoporosis Risk Estimation), may be used to screen patients to determine if a DEXA bone mineral density measurement is necessary. If DEXA is performed, the patient should be excluded from receiving the device if the DEXA bone density measured T score is $\leq$ -1.0, as the patient may be osteopenic.

PRODISC®-L Total Disc Replacement components should not be used with components of spinal systems from other manufacturers. See the surgical technique manual for step by step instructions.

Patients should be instructed in postoperative care procedures and should be advised of the importance of adhering to these procedures for successful treatment with the device.

Due to the proximity of vascular and neurological structures to the implantation site, there are risks of serious or fatal hemorrhage and risks of neurological damage with the use of this device. Serious or fatal hemorrhage may occur if the great vessels are eroded or punctured during implantation and are subsequently damaged due to breakage of implants, migration of implants, or if pulsatile erosion of the vessels occurs because of close apposition of the implants.

Ensure that the polyethylene inlay is placed in the proper direction by confirming that the rounded profile is facing anteriorly. If the polyethylene inlay is not properly directed, the snap-lock mechanism will fail to engage and the polyethylene inlay will migrate anteriorly.

If the polyethylene inlay is not securely locked, anterior displacement of the polyethylene inlay will occur. To ensure that the polyethylene inlay is securely locked within the inferior plate component, visually confirm the polyethylene inlay is locked into the inferior endplate by using a nerve hook to verify that NO STEP, and NO GAP is present at the anterior edge of the endplate.

Overloading of the spine by engaging in extreme activities (i.e., heavy weight lifting) may result in failure of the prosthesis.

Adverse Events

The following adverse events were reported during the randomized, multi-center clinical study of 212 patients treated with the PRODISC®-L Total Disc Replacement (162 randomized and 50 non-randomized) and 80 control patients.

The following table lists adverse events that occurred in the control (F), randomized PRODISC®-L (P), and non-randomized PRODISC®-L subjects (PNR) and shows the time course distribution of the occurrence of the events. No deaths were reported.

TABLE 3 Time Course of All Adverse Events

	Intra-op 0-2 days			Peri-op >2-42 days			Short Term >42-210 days			Long Term >210 days			Number of Patients Reporting (%) and Total Events					
	F	P	PNR	F	P	PNR	F	P	PNR	F	P	PNR	Fusion (n=80)		ProDisc (n=162)		ProDisc-NR (n=50)	
													# (%)	Events	# (%)	Events	# (%)	Events
ALL ADVERSE EVENTS	29	49	12	23	48	10	39	67	18	41	97	25	70 (87.5%)	256	136 (84.0%)	505	41 (82.0%)	106
ANEMIA	2	4	0	0	2	0	0	0	0	0	0	0	2 (2.5%)	2	6 (3.7%)	7	0 (0.0%)	0
BURNING OR DYSESTHETIC PAIN	2	1	0	0	1	0	0	2	0	1	4	1	3 (3.8%)	3	8 (4.9%)	8	1 (2.0%)	1
CARDIOVASCULAR	2	1	3	0	0	0	0	0	1	3	1	1	5 (6.3%)	5	2 (1.2%)	2	5 (10.0%)	5
CLINICALLY SIGNIFICANT BLOOD LOSS (>1500 CC)	2	0	0	0	0	0	0	0	0	0	0	0	2 (2.5%)	2	0 (0.0%)	0	0 (0.0%)	0
DEGENERATIVE DISEASE PROGRESSION, NON-LUMBAR	0	0	0	0	0	0	0	1	0	0	2	0	0 (0.0%)	0	3 (1.9%)	3	0 (0.0%)	0
DEGENERATIVE DISEASE PROGRESSION, OTHER LUMBAR[1]	0	0	0	0	0	0	0	3	0	0	6	0	0 (0.0%)	0	9 (5.6%)	9	0 (0.0%)	0
DERMATOLOGICAL	1	1	0	0	2	0	1	1	0	0	2	0	2 (2.5%)	3	6 (3.7%)	6	0 (0.0%)	0
DERMATOLOGICAL DRUG ALLERGY	0	1	0	0	0	0	0	0	0	0	1	0	0 (0.0%)	0	2 (1.2%)	2	0 (0.0%)	0
DIZZINESS	1	2	0	1	0	0	1	1	0	0	1	1	3 (3.8%)	3	4 (2.5%)	4	1 (2.0%)	1
DRUG ALLERGY	1	0	0	0	1	0	0	0	0	0	2	0	1 (1.3%)	1	2 (1.2%)	3	0 (0.0%)	0
DURAL TEAR	2	0	1	0	0	0	0	0	0	0	0	0	2 (2.5%)	2	0 (0.0%)	0	1 (2.0%)	1
EDEMA	0	0	0	2	2	0	1	3	1	0	3	0	3 (3.8%)	3	8 (4.9%)	9	1 (2.0%)	1
FEVER	7	8	2	3	2	0	0	0	0	0	0	0	10 (12.5%)	10	10 (6.2%)	10	2 (4.0%)	2
FRACTURE (NON-VERTEBRAL)	0	0	0	0	0	0	0	0	0	0	2	1	0 (0.0%)	0	2 (1.2%)	2	1 (2.0%)	1
GASTROINTESTINAL	14	21	6	3	6	2	3	3	0	3	5	1	22 (27.5%)	28	32 (19.8%)	45	8 (16.0%)	9
GENITOURINARY	1	6	0	1	2	0	0	3	1	2	3	1	4 (5.0%)	4	14 (8.6%)	14	2 (4.0%)	2
HEADACHE	1	7	0	1	0	0	1	1	0	2	3	3	5 (6.3%)	5	11 (6.8%)	12	3 (6.0%)	3
HERNIATED NUCLEUS PULPOSUS	0	0	0	0	0	0	0	0	0	0	1	0	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
INCONTINENCE	0	0	0	0	0	0	0	0	0	4	3	0	4 (5.0%)	4	3 (1.9%)	3	0 (0.0%)	0
INFECTION - OTHER NON WOUND RELATED	1	0	0	1	2	0	0	1	1	3	2	1	5 (6.3%)	6	5 (3.1%)	5	2 (4.0%)	2
INFECTION - SUPERFICIAL WOUND WITH INCISION SITE PAIN	0	0	0	1	0	1	0	0	0	1	0	0	2 (2.5%)	2	0 (0.0%)	0	1 (2.0%)	1
INFECTION - UTI	0	0	0	0	0	1	0	0	1	1	0	0	1 (1.3%)	1	0 (0.0%)	0	2 (4.0%)	2
INSOMNIA	1	3	0	1	0	0	1	3	0	1	2	1	4 (5.0%)	4	8 (4.9%)	8	1 (2.0%)	1
MIGRATION NOT REQUIRING SURGERY	0	0	0	0	0	0	0	3	2	1	0	0	1 (1.3%)	1	3 (1.9%)	3	2 (4.0%)	2
MIGRATION REQUIRING SURGERY	0	0	0	0	2	0	0	0	0	0	2	0	0 (0.0%)	0	4 (2.5%)	4	0 (0.0%)	0
MOTOR DEFICIT / INDEX LEVEL	0	0	0	0	0	0	0	1	0	0	4	0	0 (0.0%)	0	4 (2.5%)	5	0 (0.0%)	0
MUSCULOSKELETAL SPASMS - BACK	0	0	0	0	0	0	2	0	0	0	1	0	2 (2.5%)	2	1 (0.6%)	1	0 (0.0%)	0
MUSCULOSKELETAL SPASMS - BACK AND LEG	0	0	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.0%)	1
MUSCULOSKELETAL SPASMS - LEG	0	0	0	0	0	0	0	0	0	0	2	0	0 (0.0%)	0	2 (1.2%)	2	0 (0.0%)	0
NARCOTICS USE	0	0	0	0	1	0	1	1	1	0	0	0	1 (1.3%)	1	2 (1.2%)	2	1 (2.0%)	1
NERVE ROOT INJURY	0	1	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	0	1 (0.6%)	1	1 (2.0%)	1
NON-SPECIFIC MUSCULOSKELETAL SPASMS	1	3	0	0	3	0	0	0	0	0	1	0	1 (1.3%)	1	6 (3.7%)	7	0 (0.0%)	0
NUMBNESS INDEX LEVEL RELATED	0	0	0	0	0	0	1	0	0	0	0	0	1 (1.3%)	1	0 (0.0%)	0	0 (0.0%)	0
NUMBNESS PERIPHERAL NERVE OR NON-INDEX LEVEL RELATED	0	3	3	1	1	1	4	9	0	0	6	1	5 (6.3%)	5	17 (10.5%)	20	5 (10.0%)	5
OTHER MUSCULOSKELETAL	1	1	0	0	1	1	6	9	0	7	17	2	13 (16.3%)	15	21 (13.0%)	28	3 (6.0%)	3
OTHER*	2	3	0	1	0	0	0	2	0	5	7	2	8 (10.0%)	8	11 (6.8%)	13	2 (4.0%)	2
PAIN - BACK	0	1	1	2	3	2	10	25	4	18	32	6	27 (33.8%)	33	55 (34.0%)	65	13 (26.0%)	14
PAIN - BACK AND LOWER EXTREMITIES	0	1	0	1	4	1	5	14	2	4	16	9	10 (12.5%)	10	29 (17.9%)	38	10 (20.0%)	12
PAIN - BACK AND LOWER EXTREMITIES WITH BURNING	0	0	0	0	0	0	0	1	1	0	2	1	0 (0.0%)	0	3 (1.9%)	3	2 (4.0%)	2
PAIN - BACK AND LOWER EXTREMITIES WITH NUMB AT INDEX	0	0	0	1	1	0	1	2	0	2	1	0	4 (5.0%)	5	4 (2.5%)	4	0 (0.0%)	0
PAIN - BACK AND OTHER	0	0	0	0	1	0	2	2	0	3	5	1	5 (6.3%)	5	8 (4.9%)	8	1 (2.0%)	1
PAIN - GROIN AREA	0	0	0	0	0	0	0	2	0	0	3	0	0 (0.0%)	0	5 (3.1%)	5	0 (0.0%)	0
PAIN - INCISION SITE	0	1	0	0	1	0	3	0	0	3	0	0	6 (7.5%)	6	2 (1.2%)	2	0 (0.0%)	0
PAIN - LOWER EXTREMITIES	0	1	0	2	9	4	8	15	3	6	13	2	16 (20.0%)	22	32 (19.8%)	40	8 (16.0%)	11
PAIN - LOWER EXTREMITIES WITH NUMBNESS AT INDEX LEVEL	0	0	0	1	1	0	0	1	1	0	1	1	1 (1.3%)	1	3 (1.9%)	3	2 (4.0%)	2
PAIN OTHER (NOT BACK/HIP/LEG)	2	4	0	3	7	1	2	7	0	5	14	1	12 (15.0%)	14	25 (15.4%)	37	2 (4.0%)	3
PRURITUS	2	7	2	2	1	0	0	0	0	0	0	0	4 (5.0%)	6	8 (4.9%)	8	2 (4.0%)	2
PSYCHOLOGICAL	1	5	0	0	4	0	1	2	0	4	10	1	6 (7.5%)	6	19 (11.7%)	20	1 (2.0%)	1
PULMONARY INFECTION	0	0	0	0	0	0	0	0	0	1	0	2	1 (1.3%)	1	0 (0.0%)	0	2 (4.0%)	2
RADIOLUCENCY - GRAFT	0	0	0	0	0	0	0	0	0	1	0	0	1 (1.3%)	1	0 (0.0%)	0	0 (0.0%)	0
REFLEX CHANGE	0	0	0	0	0	0	0	0	0	0	1	0	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
RESPIRATORY	0	2	0	0	0	0	0	1	0	0	1	0	0 (0.0%)	0	4 (2.5%)	5	0 (0.0%)	0
RETROGRADE EJACULATION	1	0	0	0	1	1	0	1	1	0	0	0	1 (1.3%)	1	2 (1.2%)	2	2 (4.0%)	2
SUBSIDENCE NOT REQUIRING SURGERY	0	0	0	0	1	0	0	0	0	1	1	1	1 (1.3%)	1	2 (1.2%)	2	1 (2.0%)	1
SUBSIDENCE REQUIRING SURGERY	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
SURGERY - ADJACENT LEVEL	0	0	0	0	0	0	1	0	1	0	2	0	1 (1.3%)	1	2 (1.2%)	2	1 (2.0%)	1
SURGERY - INDEX LEVEL (REVISION)	0	1	0	0	0	0	1	0	0	3	0	0	4 (5.0%)	4	1 (0.6%)	1	0 (0.0%)	0
SURGERY - INDEX LEVEL (SUPPLEMENTAL FIXATION)	0	0	0	0	0	0	0	0	0	0	1	0	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
SURGERY - OTHER	0	0	0	1	0	0	2	1	0	0	6	3	3 (3.8%)	3	7 (4.3%)	7	3 (6.0%)	3
THROMBOSIS	0	0	0	0	0	1	0	0	0	0	0	0	0 (0.0%)	0	0 (0.0%)	0	1 (2.0%)	1
THROMBOSIS (DVT LEG)	0	0	0	1	2	0	0	0	0	0	0	0	1 (1.3%)	1	2 (1.2%)	2	0 (0.0%)	0
VESSEL DAMAGE/BLEEDING, MAJOR	1	1	0	0	0	0	0	0	0	0	0	0	1 (1.3%)	1	1 (0.6%)	1	0 (0.0%)	0
VESSEL DAMAGE/BLEEDING, MINOR	4	4	0	1	0	0	0	0	0	0	0	0	5 (6.3%)	5	4 (2.5%)	4	0 (0.0%)	0
WOUND ISSUES, OTHER	0	1	0	4	3	0	1	1	0	2	0	1	7 (8.8%)	7	5 (3.1%)	5	1 (2.0%)	1

Patients may have adverse events in more than one category and are counted once in each category in which they experience an adverse event
The "n" is the total number of patients treated, including patients with major protocol violations

[1] Four PRODISC®-L subjects reported adjacent level symptoms.

* Eight control subjects reported eight "Other" events: night sweats, lung cancer, thrombocytopenia, weight loss, increased liver enzymes, drowsiness, low magnesium, diabetes. Eleven PRODISC®-L subjects reported thirteen "Other" events: Factor V abnormality, concussion, diabetes (3), nose bleeds, gluteal hematoma, lung infiltrate, chills, low serum magnesium (2), tooth extraction, hot flashes. Two PRODISC®-L Non-randomized subjects reported two "Other" events: photophobia, trauma due to fall.

The following potential adverse events (singly or in combination) which may be expected to occur, but were not observed in the clinical trial, could also result from the implantation of the PRODISC®-L Total Disc Replacement:

Surgery Related

- Anesthetic reaction
- Bowel perforation
- Epidural hematoma
- Hernia
- Ileus requiring nasogastric tube
- Infection – peritonitis
- Peritoneal adhesions
- Pulmonary embolism
- Retroperitoneal hematoma
- Seizures
- Injury to kidneys or ureters
- Nerve damage due to surgical trauma or presence of the device, neurological difficulties, including bowel and/or bladder dysfunction, impotence, tethering of nerves in scar tissue, muscle weakness or paresthesias
- Vascular damage resulting in catastrophic or fatal bleeding
- Paralysis
- Damage to lymphatic vessels and/or lymphatic fluid exudation
- Fracture of vertebral bony structures
- Additional surgery which could include removal of the PRODISC®-L
- Failure of the device/procedure to improve symptoms and/or function
- Wear debris generation either plastic or metal leading to an adverse reaction of the local tissues that may lead to implant loosening or failure
- Death

Post Surgery

- Malpositioned implants adjacent to large arteries or veins could erode these vessels and cause catastrophic bleeding in the late postoperative period
- Expulsion or retropulsion, potentially casing pain, paralysis, vascular or neurological damage, spinal cord impingement or damage
- Implant breakage, dislodgement, or migration
- Deterioration in neurologic status
- Reflex sympathetic dystrophy
- Spondylolysis
- Spondylolisthesis
- Spinal stenosis
- Change in lordosis
- Instability of the spine
- Facet joint degeneration
- Foreign body reaction
- Calcification resulting in bridging trabecular bone and fusion
- Annular ossification

Clinical Studies

Clinical data were collected to evaluate the safety and effectiveness of the PRODISC®-L Total Disc Replacement as compared to the control device, a circumferential fusion consisting of an interbody fusion using a femoral ring allograft and a posterolateral fusion with autogenous iliac crest bone graft, combined with pedicle screw instrumentation. The purpose of the study was to determine whether the PRODISC®-L Total Disc Replacement was non-inferior to circumferential fusion. To qualify for enrollment in the study, patients met all the inclusion criteria and none of the exclusion criteria listed in the following table:

Inclusion	Exclusion
Degenerative Disc Disease (DDD) in one vertebral level between L3 and S1. Diagnosis of DDD requires: Back and/or leg (radicular pain); and Radiographic confirmation of any 1 of the following by CT, MRI, discography, plain film, myelography and/or flexion/extension films: • Instability (≥3mm translation or ≥5° angulation); • Decreased disc height >2mm; • Scarring/thickening of annulus fibrosis; • Herniated nucleus pulposus; or • Vacuum phenomenon Age between 18 and 60 years Failed at least 6 months of conservative treatment Oswestry Low Back Pain Disability Questionnaire score of at least (40%) (Interpreted as moderate/severe disability) Psychosocially, mentally and physically able to fully comply with this protocol including adhering to follow-up schedule and requirements and filling out of forms Signed informed consent	No more than 1 vertebral level may have DDD and all diseased levels must be treated Patients with involved vertebral endplates dimensionally smaller than 34.5 mm in the medial-lateral and or 2[illegible] mm in the anterior-posterior directions Known allergy to titanium, polyethylene, cobalt, chromium or molybdenum Prior fusion surgery at any vertebral level Clinically compromised vertebral bodies at the affected level due to current or past trauma Radiographic confirmation of facet joint disease or degeneration Lytic spondylolisthesis or spinal stenosis Degenerative spondylolisthesis of grade > 1 Back or leg pain of unknown etiology Osteopenia or osteoporosis: A screening questionnaire for osteoporosis, SCORE (Simple Calculated Osteoporosis Risk Estimation), will be used to screen patients to determine if a DEXA scan is required. If DEXA is required, exclusion will be defined as a DEXA bone density measured T score < -2.5. Paget's disease, osteomalacia or any other metabolic bone disease (excluding osteoporosis which is addressed above) Morbid obesity defined as a body mass index >40 or a weight more than 100 lbs. over ideal body weight Pregnant or interested in becoming pregnant in the next 3 years Active infection – systemic or local Taking medications or any drug known to potentially interfere with bone/soft tissue healing (e.g., steroids) Rheumatoid arthritis or other autoimmune disease Systemic disease including AIDS, HIV, Hepatitis Active malignancy: A patient with a history of any invasive malignancy (except non-melanoma skin cancer), unless he/she has been treated with curative intent and there has been no clinical signs or symptoms of the malignancy for at least 5 years

Following surgery, while investigators were advised to prescribe the appropriate rehabilitation program and manage its progress on a case-by-case basis, they were given certain guidelines to follow irrespective of the subject's treatment group. The guidelines

included ambulating beginning on postoperative day 1-3 with supervised use of a walker and a simple corset when out of bed (at the surgeon's discretion). Isometric leg exercises were recommended for the first two weeks postoperatively with the subsequent initiation of outpatient physical therapy. The guidelines suggested that subjects be instructed to avoid excessive bending or lifting for the first two weeks postoperatively; to begin driving, light bending, and lifting from 2-6 weeks postoperatively; and to gradually resume normal activities beginning at 6 weeks postoperatively.

Subjects were evaluated preoperatively, intraoperatively, and immediately postoperatively followed by evaluations at 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months. Complications and adverse events, device-related or not, were evaluated over the course of the clinical trial.

Safety and effectiveness was assessed in all randomized and non-randomized subjects.

The safety of the PRODISC®-L Total Disc Replacement was assessed by monitoring intra-operative and postoperative complications. Radiographs were used to monitor the occurrence of some of the adverse events and complications, including subsidence of the device into the adjacent disc, device migration, other changes in the implant, and spinal instability.

All radiographic endpoints were evaluated independently by a core laboratory and reviewed by an independent radiologist.

Overall Success was determined from data collected during the initial 24 months of follow-up. Primary outcome parameters were evaluated for all treated subjects at 6, 12, 18 and 24 months using two different composite success criteria: (1) the sponsor's proposed success criteria and (2) FDA's requested definition of Overall Success. An individual subject was considered a study success (i.e., Overall Success) if all of the following conditions were met:

Sponsor's Overall Success criteria	FDA's Overall Success criteria
Improvement in the Oswestry Disability Index (ODI) ≥ 15% at 24 months compared to the score at baseline	Improvement in the Oswestry Disability Index (ODI) ≥ 15 points at 24 months compared to the score at baseline
No reoperation required to remove or modify the PRODISC®-L implant (investigational group) or to modify the fusion site or correct a complication with an implant (control group)	No reoperation required to remove or modify the PRODISC®-L implant (investigational group) or to modify the fusion site or correct a complication with an implant (control group)
Improvement in SF-36 (24-month score – pre-operative score > 0)	Improvement in SF-36 (24-month score – pre-operative score > 0)
Neurological status improved or maintained (motor, sensory, reflex, straight leg raise)	Neurological status improved or maintained (motor, sensory, reflex, straight leg raise)
Radiographic success: • No radiographic evidence of device migration or subsidence >3mm • No extensive radiolucency/loosening (<25% of interface's length for each endplate in the investigational group; no halos or radiolucencies around the implant in the control group) • No loss of disc height > 3mm • Fusion status: no evidence of bony fusion (investigational group) or strong evidence of fusion including >50% trabecular bridging bone or bone mass maturation and increased or maintained bone	Radiographic success: • No radiographic evidence of device migration or subsidence >3mm • No extensive radiolucency/loosening (<25% of interface's length for each endplate in the investigational group; no halos or radiolucencies around the implant in the control group) • No loss of disc height > 3mm • Fusion status: no evidence of bony fusion (investigational group) or strong evidence of fusion including >50% trabecular bridging bone or bone mass maturation and increased or maintained bone

density at site and no visible gaps in the fusion mass (control group) • Motion status: o Investigational group: ROM at the implanted level maintained or improved from preoperative baseline (F/E ROM at 24 months "normal" where "normal" ROM defined as follows): - L3/L4: ≥6° (±3° error) and ≤20° (design limit) - L4/L5: ≥6° (±3° error) and ≤20° (design limit) - L5/S1: ≥5° (±3° error) and ≤20° (design limit) o Control group: no motion (<3mm translation, <5° angulation) on flexion/extension films	density at site and no visible gaps in the fusion mass (control group) • Motion status: o Investigational group: ROM at the implanted level maintained or improved from preoperative baseline (24 month F/E ROM – Preop F/E ROM ≥ 0 with ±3° measurement error applied) o Control group: no motion (<3mm translation, <5° angulation) on flexion/extension films
Non-inferiority margin: 12.5%	Non-inferiority margin: 10%

Neurological status was assessed using the following: (i) reflexes at the knee and ankle (absent/present, symmetrical/asymmetrical); (ii) motor function (bilateral or unilateral weakness. evaluated on a 5-point scale for gluteus maximus, iliopsoas, quadriceps, hamstrings, anterior tibial group, posterior tibial, extensor hallucis longus, and flexor hallucis); (iii) sensitivity to light touch (numbness, tingling in the groin, anterior thigh, medial leg, lateral leg, and lateral foot); and (iv) straight leg raise, with evaluation of cross-positive reactions.

The secondary endpoints assessed were ODI success (using ≥25%, ≥15%, and ≥15 points improvement from baseline), improvement in pain on a Visual Analog Scale (VAS) comparing baseline to 24 month post-operative score (no definition of success provided), neurological success, (motor, sensory, reflex, straight leg raise), quality of life measured with the SF-36 questionnaire (improvement of 15% at 24 months compared to baseline), and several radiographic assessments. Other outcomes measured included VAS subject satisfaction and willingness to have the same surgery again.

Subject Demographics

Seventeen (17) sites participated in the study with a total of two hundred ninety two (292) subjects enrolled and treated; the first three subjects at each center were not randomized and served as training cases. 162 subjects in the randomized treatment arm (PRODISC®-L randomized), 80 subjects in the control arm (circumferential fusion), and 50 subjects in the non-randomized treatment arm (PRODISC®-L non-randomized) were treated.

The table below shows select demographics and baseline characteristics of the investigational and control groups.

Demographic and Baseline Characteristics

	Fusion (n =80)	PRODISC®-L (Randomized) (n=162)		PRODISC®-L (Non-randomized) (n=50)
Age at Surgery (years)				
N	80	162		50
Mean (SD)	40.2 (7.6)	39.6 (8.0)		37.9 (8.0)

Gender [N (%)]				
Male	37 (46.3%)	83 (51.2%)		20 (40.0%)
Female	43 (53.8%)	79 (48.8%)		30 (60.0%)
Body Mass Index (kg/m²)				
N	80	162		49
Mean (SD)	27.4 (4.3)	26.7 (4.2)		25.9 (4.6)
Baseline Oswestry Score (/ 100)				
N	80	162		50
Mean (SD)	62.9 (63.4)	63.4 (12.6)		62.6 (11.9)
Target Level at Screening				
L3-L4	3 (3.8%)	3 (1.9%)		1 (2.0%)
L4-L5	27 (33.8%)	54 (33.3%)		14 (28.0%)
L5-S1	50 (62.5%)	105 (64.8%)		35 (70.0%)

Surgical and Hospitalization Information

The mean intra-operative time was significantly shorter in the PRODISC®-L randomized group compared with the Fusion group (121 minutes versus 219 minutes, $p<0.0001$). The mean estimated blood loss (EBL) was lower in the PRODISC®-L randomized group, compared with the Fusion group (203 cc versus 451 cc, $p<0.0001$). The length of hospital stay was also significantly shorter in the PRODISC®-L randomized group (3.5 days versus 4.4 days, $p<0.0001$). While the differences in the means for each of these parameters were statistically significant, in each case the ranges were similar so the statistical significance may not be clinically significant.

Clinical effectiveness evaluation

The primary effectiveness endpoint of this study was the difference in proportion of Overall Success between the two treatment groups. The success status of subjects was summarized by treatment group.

The population which was used to assess these endpoints consisted of all randomized subjects who completed all evaluations at the 24-month time point, regardless of when the 24-month measurements occurred.

Components of Overall Success at Month 24

	Fusion	**PRODISC®-L (Randomized)**		**PRODISC®-L (Non-randomized)**
ODI success (≥15% improvement)	46/71 (64.8%)	115/149 (77.2%)		41/48 (85.4%)
ODI success (≥15 point improvement)	39/71 (54.9%)	101/149 (67.8%)		36/48 (75.0%)
Device success (no reoperation, revision, removal or supplemental fixation)	73/75 (97.3%)	155/161 (96.3%)		50/50 (100%)
Neurological success (maintain or	57/70	135/148		40/48

improve – motor, sensory, reflex, and straight leg raise)	(81.4%)	(91.2%)		(83.3%)
SF-36 success (score improved)	49/70 (70.0%)	118/149 (79.2%)		43/48 (89.6%)
Radiographic success (using FDA's definition of ROM success)[1,5]	59/69 (85.5%)	125/143 (87.4%)		40/45 (88.9%)
Radiographic success (using Sponsor's definition of ROM success)[2,5]	59/69 (85.5%)	131/143 (91.6%)		43/45 (95.6%)
Overall Success[3]	**32/71 (45.1%)**	**94/148 (63.5%)**		**30/45 (66.7%)**
Overall Success[4]	**29/71 (40.8%)**	**79/148 (53.4%)**		**25/45 (55.6%)**

1 (24 month flexion/extension ROM – Preop flexion/extension ROM) ≥ 0 (with ± 3° measurement error applied)

2 Flexion/extension ROM at 24 months "normal", where "normal" ROM defined as follows:
- L3/L4 normal if ROM ≥ 6° (±3° error) and ≤ 20° (design limit of device)
- L4/L5 normal if ≥ 6° (±3° error) and ≤ 20° (design limit of device)
- L5/S1 normal if ≥ 5° (±3° error) and ≤ 20° (design limit of device)

3 Synthes Spine proposed criteria: Analysis conducted per the investigational protocol, including ≥15% ODI score improvement, sponsor's definition of ROM success and a non-inferiority margin of 12.5%

4 FDA requested criteria: Analysis conducted as above, except: ≥15 point ODI score improvement, FDA's definition of ROM success, and a non-inferiority margin of 10%

5 Four of the patients had a partial post-24 month analyses and radiographic analysis was completed post 24 months (range 33-45 months postoperatively).

The 95% two-sided confidence interval indicates that the Overall Success rate for the PRODISC®-L Total Disc Replacement is within the non-inferiority margin, regardless of which set of study success criteria are used.

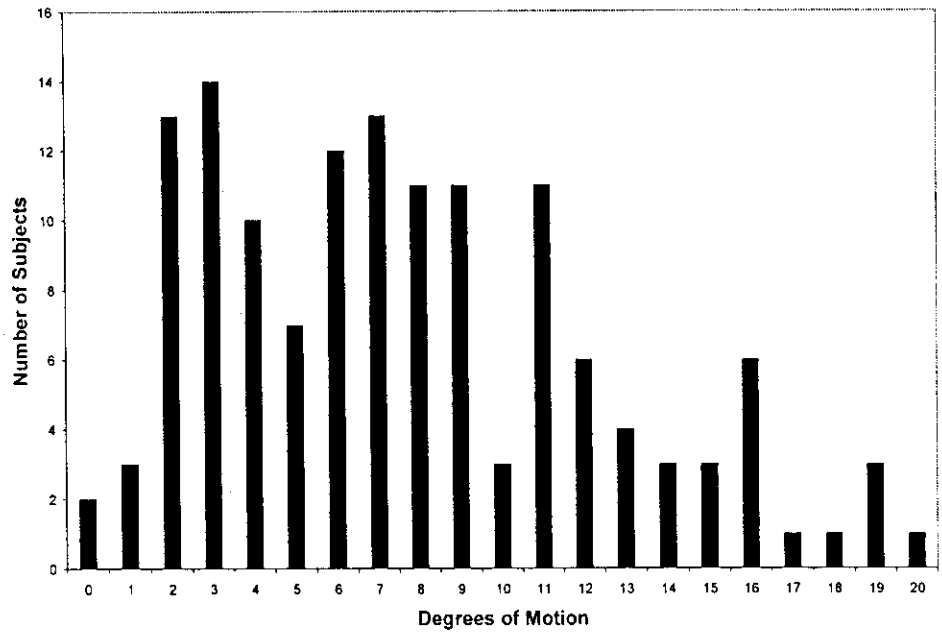
Flexion/extension range of motion (ROM) in degrees at the operative level, determined as the difference in Cobb measurements between dynamic flexion/extension lateral radiographs, was determined at 3, 6, 12, 18 and 24 months.

Time Course of Mean Flexion/Extension ROM

	Month 3	Month 6	Month 12	Month 18	Month 24
Fusion	1.0	0.9	0.9	0.8	0.7
PRODISC (Randomized)	6.3	6.1	7.0	7.1	7.7
PRODISC (Not randomized)	6.3	7.4	7.0	7.1	8.8

A histogram is provided showing the range of ROM values recorded for all randomized PRODISC®-L Total Disc Replacement subjects at 24 months. This histogram used values obtained by rounding recorded ROM for each subject to the nearest integer.

Histogram of PRODISC®-L Randomized Flexion/Extension ROM at 24 Months



An analysis of the range of motion data versus Overall Success for all PRODISC®-L randomized subjects with available range of motion data at 24 months was also performed. No statistically significant association was found between range of motion and success or failure at 24 months.

How Supplied

The PRODISC®-L Total Disc Replacement components are supplied prepackaged and sterile. The integrity of the packaging should be checked to ensure that the sterility of the contents is not compromised. Remove implants from packaging using aseptic technique, only after the correct size has been determined.

Conformance to Standards

The PRODISC-L Total Disc Replacement endplates are manufactured from CoCrMo conforming to ISO 5832-12 (1996) "Implants for surgery – Metallic materials – Part 12: Wrought cobalt-chromium-molybdenum alloy. The surfaces of both inferior and superior plates that abut against the bone are plasma sprayed with CPTI conforming ISO/DIS 5832-2 (1999) "Implants for surgery – Metallic materials– Part 2: Unalloyed titanium". The inlays are manufactured from ultra-high molecular weight polyethylene (UHMWPE) conforming to ISO 5834-2 and ASTM 648.

Device Retrieval

Should it be necessary to remove a PRODISC®-L Total Disc Replacement, please contact Synthes Spine to receive instructions regarding the data collection, including histopathological, mechanical and adverse event information.

Please note that the disc replacement device should be removed as carefully as possible in order to keep the implant and surrounding tissue intact. Also, please provide descriptive information about the gross appearance of the device in situ, as well as descriptions of the removal methods, i.e., intact or in pieces.

Limited warranty and disclaimer: Synthes Spine products are sold with a limited warranty to the original purchaser against defects in workmanship and materials. Any other express or implied warranties, including warranties of merchantability or fitness, are hereby disclaimed.

"See Directions for Use at http://products.synthes.com or call 1-800-523-0322"

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