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**CLINICAL REVIEW**

**SUMMARY**

The subject device is the Charité™ Artificial Disc, consisting of two CoCrMo alloy endplates and an UHMWPE core, indicated for spinal arthroplasty in patients with single-level lumbar degenerative disc disease (DDD) from L<sub>4</sub> to S<sub>1</sub>. The sponsor conducted a non-inferiority randomized, prospective clinical trial comparing the clinical results of treatment with the subject device and anterior interbody fusion using the BAK fusion cage. The study demonstrated that the Charité™ Artificial Disc is safe and effective in the treatment of lumbar DDD compared to anterior interbody fusion with the BAK cage.

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**REVIEW**

The subject of this review is P040006, the clinical module for M020026/M003, dated 2/13/04 and received 2/13/04.

**Regulatory History**

The Modular Shell was approved 3/4/03. The first module, M001, was filed on 3/12/03. The second module, M002, was filed 4/17/03.

**CLINICAL INFORMATION**

The subject device (as well as previous design versions) has been commercially available in other countries since 1987. The sponsor estimates that over 7,000 patients worldwide have received a Charité Artificial Disc replacement. The Waldemar Link Company in Hamburg, Germany is manufacturer of the device.

**CLINICAL TRIALS**

**INVESTIGATIONAL PLAN**

The sponsor states that five versions of the protocol were utilized in this study. The sponsor provided a summary of the changes in Volume 14, pp.1-8. The investigational plan is summarized below with the protocol changes noted in the applicable section.

**Purpose**

The stated purpose of the investigation is to evaluate the safety and effectiveness of the SB Charité™ III (SB III) compared to the BAK Interbody Fusion Device (BAK Cage) for the treatment of single-level degenerative disc disease, as per 21 CFR 812.25(a). The sponsor makes no unsubstantiated statements about expected outcomes and makes no concluding statements about the safety or effectiveness of the device.

**Study Design**

The sponsor proposed a randomized, prospective, multicenter clinical trial consisting of 341 patients with single-level DDD of the lumbar spine (L<sub>4</sub>L<sub>5</sub> or L<sub>5</sub>S<sub>1</sub>) in patients who have not previously received surgical treatment, except for a prior discectomy, laminotomy, or nucleolysis at the same level, and have failed to

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improve with conservative treatment for at least 6 months prior to enrollment. After enrollment, the patients will be randomized in a 2:1 ratio to two treatment groups: SB III or BAK control. Each investigational site has an independent block randomization schedule. There will be a maximum of 15 investigational sites. The first 5 patients at each investigational site will not be randomized but will all receive the SB III device.

**Controls** (Volume 14, Section 8.13.1.1, p.12) The patients randomized to the control treatment will undergo lumbar interbody fusion with a BAK cage.

**Intended Use**

“The Charité Artificial Disc is indicated for spinal arthroplasty in skeletally mature patients with degenerative disc disease (DDD) at one level from L<sub>4</sub> to S<sub>1</sub>. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. These DDD patients may also have up to 3mm of spondylolisthesis at the involved level. Patients receiving the Charité Artificial Disc should have had at least 6 months of conservative treatment prior to implantation of the Charité Artificial Disc; these treatments may include discectomy, laminotomy/ectomy (without accompanying facetotomy), or nucleolysis at the same level to be treated.”

**Device Description**

The subject device is the Charité™ Artificial Disc. The device consists of two endplates manufactured from CoCrMo alloy (ASTM F75) and an UHMWPE sliding core (ASTM F648). The bi-convex core articulates between the two concave endplates. The endplates are available in 5 sizes, and each size is available in 4 angles: plane-parallel (0°) and oblique (5°, 7.5°, and 10°). The undersurface of the endplates is slightly convex and has 6 tooth-like projections that anchor the plates to the bone. The UHMWPE core is available in 5 diameters, and each is available in 5 heights for sizes 1-3, and 4 heights for sizes 4-5. The core also has a radio-opaque CoCr alloy wire for x-ray visualization.

Charite Endplates			
Size	AP width (mm)	Lateral width (mm)	Angles (degrees)
1	23	28.5	0, 5, 7.5, 10
2	25	31.5	0, 5, 7.5, 10
3	27	35.5	0, 5, 7.5, 10
4	29	38.5	0, 5, 7.5, 10
5	31	42.0	0, 5, 7.5, 10

Charite Cores		
Size	Diameter (mm)	Heights (mm)
1	23	7.5, 8.5, 9.5, 10.5, 11.5
2	25	7.5, 8.5, 9.5, 10.5, 11.5
3	27	7.5, 8.5, 9.5, 10.5, 11.5
4	29	8.5, 9.5, 10.5, 11.5
5	31	8.5, 9.5, 10.5, 11.5

There were three generations of the subject device: Charité I, Charité II, and Charité III. The Charité I and II devices had 1mm thick stainless steel endplates. The Charité I device was implanted in 13 patients beginning in 1984, but had a problem with endplate subsidence, attributed to the small surface area of the implant. The Charité II had a new oval-shaped endplate design with a large surface area, and these were implanted in 58 patients beginning in 1985. However, the endplates of these devices fractured, and this problem was attributed to the non-forged stainless steel material. The Charité III design was introduced in 1987. The device design incorporated changes in endplate material (CoCrMo alloy); number, shape and position of the endplate teeth; addition of additional endplate sizes and angles; and changes in the core shape and size. The device has been named the SBIII, SBC, Link SBC, and others. In June 2003, DePuy Spine acquired the device.

**Statistical Plan**

The study has been designed as a non-inferiority trial.

**Success definition:**

The protocol (Volume 2, p.38) states that the individual patient will be determined to be a success if all of the following are found:

1. Improvement in the Oswestry Disability Index  $\geq 25\%$  at 24 months compared to the score at baseline.
2. No device failures requiring revision, re-operation, or removal.
3. Absence of major complications, defined as major blood vessel injury, neurological damage, or nerve root injury.
4. Maintenance or improvement in neurological status at 24 months, with no new permanent neurological deficits compared to baseline.

The study was designed as a non-inferiority trial with a  $d = 0.15$ .

$$H_0: \mu_s = \mu_t + d$$

$$H_1: \mu_c < \mu_t + d$$

$\mu_s$ : Clinical success rate in the BAK Cage Control group

$\mu_c$ : Clinical success rate in the SB Charité™ III group

$d$ : Clinically significant difference between the treatment groups.  $d = 0.15$

Because the  $d$  includes confidence intervals, the observed success rate for the SB Charité™ III group could be no more than 4.9% lower than the success rate for the BAK Cage Control group to conclude that the two groups are equivalent.

**Sample Size Justification:**

The sponsor assumed a 70% success rate for both treatment groups.

$$d = 0.15$$

$$\alpha = 0.05$$

$$\beta = 0.80$$

The estimated sample size was 174 patients for the treatment group and 87 patients for the control group, or 261 patients total. With a 10% dropout rate, the treatment group sample size is 194 patients and the control group is 97 patients, for a total of 291 patients. Assuming 5 training cases per site at 15 sites, the total is 366 patients (269 investigational and 97 control).

**Analysis Populations:**

The sponsor also defined the following populations for analysis:

- ?? Intent-to-Treat (ITT) population: all patients who were randomized in the study and had either a 24-month follow-up evaluation or had been declared an “early discontinuation” (i.e., lost to follow-up). Patients who were not yet due for follow-up or those who were overdue for the 24-month evaluation were not included in the ITT group.
- ?? All Randomized Subjects population: all patients enrolled.
- ?? Completers population: patients who were evaluated at 24 months regardless of whether the visit was within the defined evaluation time window (22 months to 26 months)
- ?? Completers In-Window population: patients who had the 24-month evaluation within the defined evaluation time window (22 months to 26 months)
- ?? Safety population: all patients who were randomized and received treatment.

**Missing Data:**

Patients with incomplete or missing data were classified as failures for the efficacy analysis. Missing values were ignored for the analysis of secondary endpoints, summaries of baseline characteristics, and other summaries.

**Endpoints**

Primary Endpoints:

- ?? Oswestry Score ( $\mu$ ) at 24-months or later.

Secondary Endpoints:

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- ?? Pain VAS improvement of =20mm
- ?? SF-36 improvement =15%
- ?? Disc height (lateral x-ray)
- ?? Displacement or migration of the device
- ?? Radiolucency around the implant for Charité patients at 24 months

**Interim Analyses**

None.

**Inclusion/Exclusion Criteria** (Volume 14, pp.17-14)

<b>Inclusion</b>	<b>Exclusion</b>
<ul style="list-style-type: none"> <li>?? Male or female</li> <li>?? Age 18-60 years</li> <li>?? Symptomatic degenerative disc disease with objective evidence of lumbar DDD by CT or MR scan, followed by discogram</li> <li>?? Single level disease at L<sub>4</sub>L<sub>5</sub> or L<sub>5</sub>S<sub>1</sub></li> <li>?? Minimum of 6 months of unsuccessful conservative treatment</li> <li>?? Oswestry Low Back Pain Disability Questionnaire =30 points</li> <li>?? Patient a surgical candidate for an anterior approach to the lumbar spine (&lt;3 abdominal surgeries)</li> <li>?? Back pain at the operative level only (by discogram)</li> <li>?? Leg pain and/or back pain in the absence of nerve root compression, per MRI or CT scan, without prolapse or narrowing of the lateral recess.</li> <li>?? VAS =40mm</li> <li>?? Able to comply with protocol</li> <li>?? Informed consent</li> </ul> <p>DDD is defined as discogenic back pain with degeneration of the disc as confirmed by history and radiographic studies with one or more of the following factors:</p> <ul style="list-style-type: none"> <li>o Contained herniated nucleus pulposus</li> <li>o Facet joint degeneration/changes</li> <li>o Decreased disc height by =2mm, and/or</li> <li>o Scarring/thickening of ligamentum flavum, annulus fibrosus, or facet joint capsule</li> </ul>	<ul style="list-style-type: none"> <li>?? Previous or other spinal surgery at any level, except prior discectomy, laminotomy, laminectomy, or nucleolysis at the same level</li> <li>?? Multiple level degeneration</li> <li>?? Previous trauma to the L<sub>4</sub>, L<sub>5</sub>, or S<sub>1</sub> levels in compression or burst</li> <li>?? Non-contained or extruded herniated nucleus pulposus</li> <li>?? Mid-sagittal stenosis of &lt;8mm (by CT or MR)</li> <li>?? Spondylolisthesis &gt;3mm</li> <li>?? Lumbar scoliosis (&gt;11° sagittal plane deformity)</li> <li>?? Spinal tumor</li> <li>?? Active systemic or surgical site infection</li> <li>?? Facet joint arthrosis</li> <li>?? Arachnoiditis</li> <li>?? Isthmic spondylolisthesis</li> <li>?? Chronic steroid use</li> <li>?? Metal allergy</li> <li>?? Pregnancy</li> <li>?? Autoimmune disorders</li> <li>?? Psychosocial disorders</li> <li>?? Morbid obesity (BMI &gt;40)</li> <li>?? Bone growth stimulator use in spine</li> <li>?? Investigational drug or device use within 30 days</li> <li>?? Osteoporosis or osteopenia or metabolic bone disease</li> <li>?? Positive single or bilateral straight leg raising test</li> </ul>

**Study Treatments** (Volume 14, Section 8.13.1.1, p.22)

**SB Charité™ III Treatment Group**

All investigational group patients will undergo a discectomy and implantation of the SB Charité™ III device through an anterior retroperitoneal approach

**BAK Interbody Fusion Device Control Treatment Group**

Patients randomized to the control group will have an anterior lumbar interbody fusion at one or two contiguous levels (L<sub>2</sub>-S<sub>1</sub>) with autogenous bone grafting and stabilization with the BAK Cage using the anterior retroperitoneal approach.

### **Postoperative Protocol**

The investigational and control groups will have the same postoperative protocol. Lumbar strengthening (“stabilization therapy”) begins at 2-4 weeks postop. No lifting or bending for 6 months.

**Evaluations** (Volume 14, Section 8.31.1.1, pp.23) The protocol specifies that patient assessments will be performed preoperatively, and postoperatively prior to discharge, 6 weeks ( $\pm 2$  weeks), 3 months ( $\pm 2$  weeks), 6 months ( $\pm 1$  month), 12 months ( $\pm 1$  month), 24 months ( $\pm 2$  months) (schedule of evaluations, Section 8.4.1, Table 9).

### **Clinical Evaluation**

The following clinical assessments will be performed:

- ?? Work status: Baseline, 6 wks, 3 mo, 6 mo, 12 mo, 24 mo
- ?? Visual Analog Scale (VAS) for Pain: Baseline, 6 wks, 3 mo, 6 mo, 12 mo, 24 mo
- ?? Oswestry Disability Index (ODI): Baseline, 6 wks, 3 mo, 6 mo, 12 mo, 24 mo  
Each question is scored on a 6-point scale. The responses are added, then doubled, and expressed as a percentage. ODI are rated as follows: 0-20 minimal disability; 20-40 moderate disability; 40-60 severe disability; and  $>60$  severely disabled/bed-bound.
- ?? SF-36 Health Related Quality of Life Survey: Baseline, 6 mo, 12 mo, 24 mo  
Neurological status: Baseline, 6 wks, 3 mo, 6 mo, 12 mo, 24 mo
- ?? Range of Motion: Baseline, 6 mo, 12 mo, 24 mo
- ?? History and physical examination: Baseline, 24 mo
- ?? Adverse events: Postop, 6 wks, 3 mo, 6 mo, 12 mo, 24 mo

### **Radiographic Evaluation**

- ?? X-rays—AP, lateral, flexion/extension laterals: Within 6 mo of enrollment, postoperatively at 6 wks, 3 mo, 6 mo, 12 mo, 24 mo

All radiographs will be evaluated by the investigator and another evaluator at that investigational site. If there disagreements, a third evaluator will review the films. In the 4/5/00 protocol version, the protocol was modified to require all radiographic evaluations to be performed by a core laboratory. The radiographic evaluation protocol was provided in Volume 14, Section 8.13.1.2. The recommended radiographic technique was provided. The radiographs are scanned into the computer, and all calculations are made with the BioQuant Image Analysis System software program.

The radiographic criteria for fusion were defined as follows:

- ?? Absence of radiolucent lines around  $\geq 50\%$  of the assembly
- ?? Translation motion  $< 3\text{mm}$  (on flexion/extension), and
- ?? Angulation motion  $< 5$  degrees (on flexion/extension)

Device migration or displacement was defined as movement  $> 3\text{mm}$  (the measurement error for plain radiographs).

### **U.S. CLINICAL TRIAL RESULTS**

Two related U.S. studies of the subject device are described below. The Pivotal Study was the prospective, randomized, controlled, multicenter IDE clinical trial. The Continued Access Study was the prospective, uncontrolled, multicenter registry of patients implanted with the device under continued access. For the Pivotal Trial, the database closure date was 1/16/04.

Summary of U.S. Clinical Trials		
	Pivotal Study	Continued Access Study
Design	Multicenter Training arm (5 pts/site) Randomized arm ?? 2:1 investigational:control 24-month follow-up	Multicenter Registry 24-month follow-up

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Sites	15	15
Subjects	Approved: 194:97 + 75 training cases 375 enrolled ?? 71 training arm (Charité) ?? 205 randomized (Charité) ?? 99 randomized (BAK control)	615 approved 350 enrolled (approximately) 71 (with >12 months follow-up)
Enrollment period	Training: 3/21/00 – 5/22/01 Randomized: 5/16/00 – 4/24/02	5/17/02 to present
Investigational Rx	Charité Artificial Disc	Charité Artificial Disc
Control Rx	BAK Cage	None

**Study Population**

There were 71 training patients implanted with the Charité Artificial Disc. There were 304 randomized patients, 205 implanted with the Charité Artificial Disc and 99 fused with the BAK Cage. In addition, there were 71 patients implanted with the Charité Artificial Disc in the continued access study. The training cases will be analyzed separately from the randomized patients.

The sponsor divided the patients into two analysis groups: the Intent-To-Treat (ITT) group and the All Randomized Subjects group. The ITT group consists of all treated patients who were treated with only the patients who died or were discontinued. The All Randomized Subjects group consists of all patients enrolled into the study. The All Randomized Subjects analysis group consists of 304 patients (205 Charité patients and 99 BAK patients). The ITT group consists of 267 patients (182 Charité patients and 85 BAK patients).

The mean age of the study group was 39.5 years (19-60 years) in the Charité group, and 40.1 years (20-60 years) in the BAK group. There were 83 (46%) men and 99 (54%) women in the Charité group and 47 (55%) men and 38 women (45%) in the BAK group. The demographic data are reproduced in the following table.

<b>ITT Population Characteristics</b>		
	<b>Charité Artificial Disc</b>	<b>BAK Cage</b>
N	182	85
Sex, Men (%)	83 (46%)	47 (55%)
Women (%)	99 (54%)	38 (45%)
Age, mean	39.5	40.1
Range	19-60	20-60
Age Category >45 years	41 (23%)	28 (33%)
Age Category ≤45 years	141 (77%)	57 (67%)
Level L <sub>4</sub> L <sub>5</sub>	53 (29%)	28 (33%)
Level L <sub>5</sub> S <sub>1</sub>	129 (71%)	57 (67%)

There was no significant difference in the duration of prior conservative treatment for DDD: 33.7 months for the Charité group and 27.0 months for the BAK group. There were 62 patients (34%) in the Charité group and 27 patients (32%) in the BAK group who had undergone previous surgical treatment (Appendix 1, Table 13.1). There was one patient in each group (2% and 4%, respectively) who had osteoporosis based on DXA.

**Surgical variables**

<b>ITT Surgical Procedures</b>		
	<b>Charité Artificial Disc</b>	<b>BAK Cage</b>
N	182	85
Level L <sub>4</sub> L <sub>5</sub>	53 (29%)	28 (33%)
Level L <sub>5</sub> S <sub>1</sub>	129 (71%)	57 (67%)

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The operative times were 111 minutes and 115.3 minutes, respectively for the Charité and the BAK groups (p=0.5462). The estimated blood loss was 207cc and 224cc, respectively (p=0.6012).

For the Charité group, the implant configurations (craniad/caudad endplates) were as follows: 109 oblique/oblique; 12 oblique/parallel; 54 parallel/oblique; and 30 parallel/parallel. The implant component sizes were as follows:

<b>Charite Artificial Disc Implanted (Table 17.2)</b>					
<b>Size</b>	<b>Cephalad Endplates</b>		<b>Caudad Endplates</b>		<b>Core</b>
	Parallel	Oblique	Parallel	Oblique	
1	0	0	0	0	0
2	6	11	6	11	17
3	54	77	24	107	131
4	24	33	12	45	57
5	0	0	0	0	0

For the 99 randomized control group patients, the cage sizes were as follows:

<b>Lengths:</b>	61 20mm	<b>Diameters:</b>	1 11mm
	24 24mm		17 13mm
			50 15mm
			17 17mm

**Patient Accounting**

There were 177 Charité patients (86%) and 78 BAK patients (79%) who were evaluated at 24 months. There were 5 (3%) and 7 (8%) patients, respectively, who discontinued early from the study for the following reasons: patient non-compliance (6), voluntary withdrawal (3), lost to follow-up (left the U.S.) (1), patient refusal (1), death (1). There were 18 patients (10 Charité and 8 BAK) who were overdue for their 24-month evaluation, and 19 patients (13 Charité and 6 BAK) who were not yet due for the 24-month follow-up. Of the 205 Charité patients, 3 patients had not reached the 24-month evaluation time point at the time of database closure, 1/16/04. Therefore, the theoretical number of patients due at the 24-month time point for the Charité group was 202 patients.

<b>Patient Populations</b>				
	<b>Randomized Study</b>			<b>Continued Access</b>
	Training Arm	Charité Artificial Disc	BAK Cage	
Enrolled	71	205	99	71
All Randomized		205	99	
Not overdue for 24-month		13 (6%)	6 (6%)	
<b>Completers</b>		<b>177 (86%)</b>	<b>78 (79%)</b>	
<b>Early Discontinuation</b>		<b>5 (2%)</b>	<b>7 (7%)</b>	
<b>ITT</b>		<b>182 (89%)</b>	<b>85 (86%)</b>	
Overdue for 24-month		10 (5%)	8 (8%)	

The sponsor also defined the following populations for analysis:

- ?? All Randomized Subjects population: all patients enrolled.
- ?? Intent-to-Treat (ITT) population: all patients who were randomized in the study and had either a 24-month follow-up evaluation or had been declared an "early discontinuation" (i.e., lost to follow-up). Patients who were not yet due for follow-up or those who were overdue for the 24-month evaluation were not included in the ITT group.
- ?? Completers population: patients who were evaluated at 24 months regardless of whether the visit was within the defined evaluation time window (22 months to 26 months)
- ?? Completers In-Window population: patients who had the 24-month evaluation within the defined evaluation time window (22 months to 26 months)
- ?? Safety population: all patients who were randomized and received treatment.

The patients were categorized as “early discontinuations” if they were non-compliant with the investigational protocol, voluntarily withdrew from the study, refused to return for follow-up, or died. In the Charité group, there were 5 patients who were early discontinuations: 2 patients who were non-compliant, 1 voluntary withdrawal, 1 refusal to return for follow-up, and 1 death. For the BAK group, there were 7 patients who were early discontinuations: 4 patients who were non-compliant, 2 voluntary withdrawals, and 1 lost to follow-up (left the U.S. and unable to return). These early discontinuations were infrequent and were more frequent in the BAK control group (7% v. 2%).

Because the sponsor closed the database before the end of the 24-month evaluation time window, there are some patients who have reached the 24-month time point but are not outside the 24 month  $\pm$  2 month time window. There are 10 (5%) Charité and 8 (8%) BAK patients in this “Not Yet Overdue” category. These have been eliminated from the ITT population.

Thus, the ITT group (182 Charité patients and 85 BAK patients) consisted of All Randomized Subjects who either returned for follow-up within the 24-month evaluation time window (158 Charité patients and 72 BAK patients), or outside the 24-month time window (19 Charité patients and 6 BAK patients), as well as those categorized as “early discontinuations” (5 Charité patients and 7 BAK patients).

There were 19 patients (13 patients, or 6%, in the Charité group and 8 patients, or 6%, in the BAK group) who were “not yet overdue” for the 24-month follow-up evaluation, i.e., they had reached the 24-month evaluation time point but were still within the 24-month evaluation time window ( $\pm$ 2 months).



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Patient & Data Accountability Appendix 1, Tables 4-6														
	Post-op		6 wks		3 mo		6 mo		12 mo		24 mo		24+ mo	
PATIENTS	Charite	BAK/C	Charite	BAK/C	Charite	BAK/C	Charite	BAK/C	Charite	BAK/C	Charite	BAK/C	Charite	BAK/C
Theoretically due	205	99	205	99	205	99	205	99	205	99	202*	96	205	96
Deaths	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Failures	3	1	3	1	3	1	3	1	7	4	7	7	11	8
Withdrawn	4	7	4	7	4	7	4	7	4	7	4	7	4	7
Not yet overdue	0	0	0	0	0	0	0	0	0	0	9	3	9	63
Expected	198	91	198	91	198	91	198	91	194	88	182	79	178	78
Missed	2	1	4	1	11	3	12	6	12	9	26	14	6	6
Actual	196	90	194	90	187	88	186	85	182	79	156	65	172	72
% follow-up	98.9	98.9	98.0	98.9	94.4	96.7	93.9	93.4	93.8	89.8	85.7	81.0	96.6	92.3
DATA	Charite	BAK/C	Charite	BAK/C	Charite	BAK/C	Charite	BAK/C	Charite	BAK/C	Charite	BAK/C	Charite	BAK/C
Theoretically due	205	99	205	99	205	99	205	99	205	99	202*	96	205	96
Expected (denominator)	<b>198</b>	<b>91</b>	<b>198</b>	<b>91</b>	<b>198</b>	<b>91</b>	<b>198</b>	<b>91</b>	<b>194</b>	<b>88</b>	<b>182</b>	<b>79</b>	<b>178</b>	<b>78</b>
Oswestry	205	99	197	91	189	<b>93</b>	189	88	186	80	178	78		
%	100.0	100.0	99.5	100.0	95.5	100.0	95.5	96.7	95.9	90.9	97.8	98.7		
Neuro	205	99	197	<b>97</b>	192	<b>94</b>	190	88	187	81	178	79		
%	100.0	100.0	99.5	100.0	97.0	100.0	96.0	96.7	96.4	92.0	97.8	100.0		
Pain VAS	205	99	196	<b>92</b>	188	<b>93</b>	188	87	185	79	179	78		
%	100.0	100.0	99.0	100.0	94.9	100.0	94.9	95.6	95.4	89.8	98.4	98.7		
SF-36	185	92	178	79	168	85	166	76	160	68	144	62		
%	90.2	92.3	89.9	86.8	94.4	93.4	83.8	83.5	82.5	77.3	79.1	78.5		
X-rays	199	95	195	<b>95</b>	187	<b>93</b>	186	86	184	82	179	78		
%	97.1	95.9	98.5	100.0	94.4	100.0	93.9	94.5	94.8	93.2	98.4	98.7		
Complete	181	89	170	78	162	83	162	74	156	66	139	60		
%	88.3	89.9	85.9	85.7	81.8	91.2	81.8	81.3	80.4	75.0	76.4	75.9		

\* Of the 205 enrolled Charité patients, 3 patients had not reached the 24-month evaluation time point at the time of database closure, 1/16/04. Therefore, the theoretical number of patients due at the 24-month time point for the Charité group was 202 patients.

The data accountability follow-up rates were calculated as follows Rate = Actual data / Expected . Except at the Post-Op time point, Rate = Actual data / Theoretical.

## **Results**

### **?? Primary Endpoint**

#### **OVERALL SUCCESS**

Individual patient success was defined as a patient with all of the following conditions:

- ?? Improvement >25% Oswestry at 24 months compared to baseline
- ?? No device failures requiring revision, reoperation or removal  
No pseudarthrosis (control group)
- ?? Absence of major complication, defined as vessel injury, neurological damage, or nerve root injury
- ?? Maintenance or improvement in neurological status at 24 months, with no permanent neurological deficits compared to baseline

The overall success rates for the Charité and the BAK groups were 63% and 53%, respectively, for the ITT population ( $p < 0.0001$ ). The overall success rates for the Completers and Completers In-Window populations were nearly identical.

<b>Overall Success, Table 19</b>			
	<b>Charité Artificial Disc</b>	<b>BAK Cage</b>	<b>p value</b>
N	182	85	
ITT population	114 (63%)	45 (53%)	<0.0001
N	177	78	
Completers	115 (65%)	46 (59%)	0.0005
N	158	72	
Completers In-Window	101 (64%)	42 (58%)	0.0015

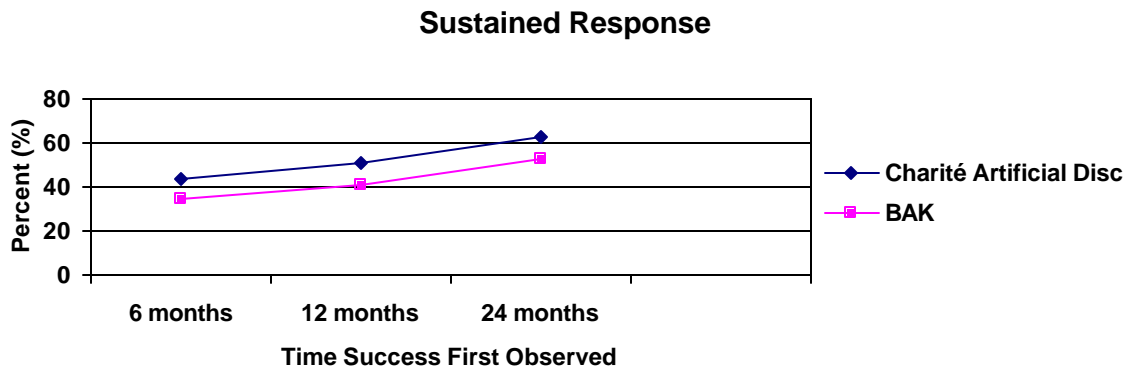
<b>Success Rates, Table 20</b>			
	<b>Charité Artificial Disc</b>	<b>BAK Cage</b>	<b>p value</b>
N	182	85	
Oswestry success (>25% improvement)	127 (70%)	49 (58%)	0.0540
Device failure success (none)	174 (96%)	77 (91%)	0.1632
Major complication success (none)	180 (99%)	84 (99%)	1.0000
Neurological deterioration success (none)	160 (88%)	74 (87%)	0.8437

The sponsor performed sensitivity analyses for the primary efficacy success endpoints (Section 8.4.2.7, Statistics, p.27; Section 8.4.4, Effectiveness, p.39). These included analyses of the ITT subjects with non-completers considered to be failures; ITT subjects with any 24-month follow-up; ITT subjects with 24-month follow-up within the 24-month time window; “last observation carried forward,” or LOCF, for All Randomized Subjects; LOCF for ITT; LOCF with discontinuations as failures; overall LOCF for overdue patient. LOCF was performed for All Randomized Patients and All Randomized Patients with discontinuations considered failures. For all of these analyses, the overall success rate for the Charité Artificial Disc Group ranged from 63% to 68%, and the overall success rate for the BAK Group ranged from 48% to 54% (see Tables 21a and 21b). An analysis was also performed removing the neurological component of success, and again showed a higher proportion of success for non-completers, slightly higher in the Charité Artificial Disc Group.

The overall success rate for the Charité Artificial Disc Group is sustained over time. A repeated measures model demonstrated that the success rates for the ITT groups at 6 months, 12 months and 24 months were 69.2%, 67.6%, and 64.2% for the Charité Group, and 47.8%, 58.8%, and 54.7% for the BAK Group (see Table 22). An analysis of the time to sustained response, i.e., the first time when success for the BAK Group was observed and continued through 24 months, was performed. For the Charité Group, the times to

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first response at 6 months, 12 months and 24 months were 44%, 51%, and 63%, and for the BAK Group they were 35%, 41%, and 53%.



Subgroup and covariate analyses were performed (see Table 23.1). The following factors were found to be not significant at the 0.15 level: age, baseline Oswestry score, gender, operative level, use of hormone replacement therapy, and use of pain medication. The following factors were found to be associated with the outcome: body mass index (but no treatment interaction); current activity (better in active patients in the Charité group, and better in inactive patients in the BAK group); osteopenia (Charité performed better than BAK; however, this involved only 15 total patients); and study site.

There were no significant differences in the success rates for the individual components of the Overall Success definition at 24 months:

**OSWESTRY SUCCESS**

?? Improvement >25% Oswestry at 24 months compared to baseline

The Oswestry success rates for the Charité and the BAK groups were 70% and 58%, respectively, for the ITT population (p=0.0540).

<b>Oswestry Success Defined as &gt;25% Improvement, Table 20.1a</b>			
	<b>Charité Artificial Disc</b>	<b>BAK Cage</b>	<b>p value</b>
N	182	85	
ITT population	127 (70%)	49 (58%)	0.0540
N	177	78	
Completers	127 (72%)	49 (63%)	0.1860
N	158	72	
Completers In-Window	112 (71%)	46 (64%)	0.2886

**DEVICE FAILURES SUCCESS**

?? No device failures requiring revision, reoperation or removal

?? No pseudarthrosis (BAK Control Group)

The Device Failure success rates for the Charité and the BAK groups were 96% and 91%, respectively, for the ITT population (p=0.0490).

<b>Device Failure Success Defined No Device Failure, Table 20.1a</b>
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	<b>Charité Artificial Disc</b>	<b>BAK Cage</b>	<b>p value</b>
N	182	85	
ITT population: Failures	8 (4%)	8 (9%)	0.1632
ITT population: Successes	174 (96%)	77 (91%)	
N	177	78	
Completers	170 (96%)	71 (91%)	0.1350
N	158	72	
Completers In-Window	153 (97%)	66 (92%)	0.1030

**MAJOR COMPLICATIONS SUCCESS**

?? Absence of major complication, defined as vessel injury, neurological damage, or nerve root injury

The Major Complications success rates for the Charité and the BAK groups were 99% and 99%, respectively, for the ITT population (p=1.000).

<b>Complications Success Defined as No Major Complication, Table 20.1a</b>			
	<b>Charité Artificial Disc</b>	<b>BAK Cage</b>	<b>p value</b>
N	182	85	
ITT population	180 (99%)	84 (99%)	1.0000
N	177	78	
Completers	175 (99%)	77 (99%)	1.0000
N	158	72	
Completers In-Window	157 (99%)	71 (99%)	0.5290

**NEUROLOGICAL SUCCESS**

?? Maintenance or improvement in neurological status at 24 months, with no permanent neurological deficits compared to baseline

The Neurological success rates for the Charité and the BAK groups were 88% and 87%, respectively, for the ITT population (p=0.8437).

The sponsor performed subgroup and covariate analyses. The following were found to be not significant: age (=45 years v. >45 years), baseline Oswestry, gender, operative level, use of hormone replacement therapy, and use of pain medication. The following were found to be associated with the outcome as either a main effect or in the interaction term: body mass index, current activity level, osteopenia, and study site.

<b>Neurological Success Defined As No Deterioration of Neurological Status, Tables 20.1a and 29.1</b>			
	<b>Charité Artificial Disc</b>	<b>BAK Cage</b>	<b>p value</b>
N	182	85	
ITT population	160 (88%)	74 (87%)	0.8437
N	177	78	
Completers	160 (90%)	74 (95%)	0.3239
N	158	72	

Completers In-Window	144 (91%)	68 (94%)	0.4422
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?? **Secondary Endpoints**

**OSWESTRY DISABILITY INDEX**

The mean Oswestry score by study population, by follow-up time, by treatment group, and the changes from baseline were analyzed.

Both the Charité and the BAK group patients experienced significant improvements in their ODI from baseline at the 6-week, 3-month, 6-month, 12-month, and 24-month evaluation timepoints. The Charité group patients had a significantly greater change in the ODI at the 6-week, 3-month and 6-month time points, although the differences were not significant at the later timepoints.

<b>Oswestry Disability Index ITT Population, Table 27.1</b>						
	<b>Baseline</b>	<b>6 wk</b>	<b>3 mo</b>	<b>6 mo</b>	<b>12 mo</b>	<b>24 mo</b>
Charité, n	182	174	168	170	169	177
ODI	49.8	37.4	29.6	27.1	25.9	25.8
Change*		-22.9	-39.5	-45.5	-48.3	48.9
From baseline, p		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
BAK, n	85	78	81	76	72	79
ODI	51.7	43.7	36.7	34.8	30.9	30.1
Change*		-12.8	-26.7	-32.4	-39.9	-43.4
From baseline, p		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Between groups, p		0.0485	0.0087	0.0126	0.1197	0.3407

\*a negative change indicates an improvement in the ODI.

The number of patients who achieved greater than 25% improvement in the ODI from baseline as also greater in the Charité group patients at the 6-week, 3-month and 6-month time points, but were not significantly different at the later timepoints.

<b>Improvement in Oswestry Scores from Baseline (= 25% Improvement), Table 26.1</b>					
	<b>6 wk</b>	<b>3 mo</b>	<b>6 mo</b>	<b>12 mo</b>	<b>24 mo</b>
Charité, n	174	168	170	169	177
Improved	80 (46%)	107 (64%)	121 (71%)	120 (71%)	128 (72%)
Charité, n	78	81	76	72	79
Improved	24 (31%)	37 (46%)	41 (54%)	47 (64%)	49 (63%)
Between groups, p	0.0269	0.0091	0.0130	0.3637	0.1860

**NEUROLOGICAL STATUS**

<b>Neurological Status ITT Analysis, Table 29.1</b>		
	<b>Charité Group</b>	<b>BAK Group</b>
N	182	85
No change	131 (77%)	58 (76%)
Significantly improved	5 (3%)	5 (7%)
Slightly improved	27 (16%)	7 (9%)
Slightly deteriorated	7 (4%)	3 (4%)
Significantly deteriorated	1 (1%)	3 (4%)

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Mixed response	0	0
Total	171	76
Missing	11	9

**PAIN VISUAL ANALOG SCALE** (Tables 30.1-31.2)

The sponsor provided the Pain VAS scores for both groups at each follow-up time point. The mean change from baseline (measured at 6 weeks) varied from -35.9 to -41.1 for the Charité group and from -28.6 to -35.1 in the BAK group. There were 128 (74%) Charité patients who were Pain VAS successes (=20mm improvement from baseline) compared to 49 (62%) BAK patients (p=0.0759).

<b>Pain VAS ITT Analysis, Table 31.1</b>		
	<b>Charité Group</b>	<b>BAK Group</b>
N	182	85
Significant improvement (=20mm)*	128 (74%)	49 (62%)
Some Improvement	22 (13%)	11 (14%)
No change (-3mm to +3mm)	3 (2%)	6 (8%)
Deterioration (≥3mm)	21 (12%)	13 (16%)
Total	174	79
Missing	8	6

\* Success = =20mm improvement

**QUALITY OF LIFE SF-36** (Tables 32.1-33.2)

For the component SF-36 scores, 99 (73%) Charité patients and 41 (66%) BAK patients had a 15% or greater improvement in the Physical Composite Score (PCS) at 24 months, and 68 (50%) and 34 (55%) patients had a 15% improvement, for the Mental Composite Score (MCS), respectively. These were not significantly different (p=0.3475 and 0.4959, respectively).

**DISC HEIGHT**

In the Charité group, there were no patients who had a decrease in disc height greater than 3mm at 24 months. There were 3 patients in the BAK group who lost more than 3mm in disc height (4%).

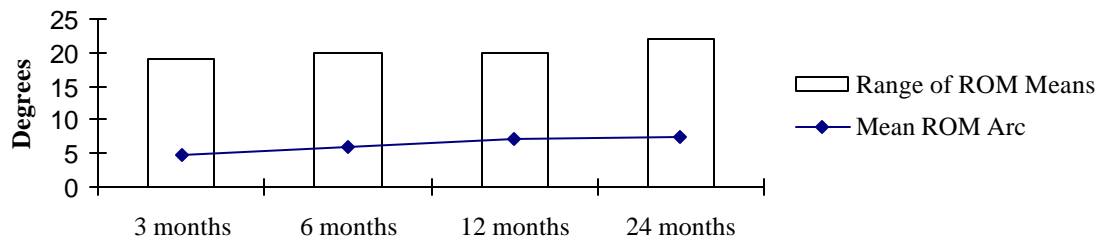
**RANGE OF MOTION** (Tables 35.1)

The vertebral range of motion measured on the lateral flexion and extension views using the Cobb method at the operated level was measured at 3, 6, 12, and 24 months. At all intervals, the Charité Artificial Disc demonstrated near-physiologic ROM (mean). The mean ROM was 4.9, 6.0, 7.0 and 7.4 degrees, respectively.

<b>Vertebral Range of Motion Table 35.1</b>				
	<b>3 months</b>	<b>6 months</b>	<b>12 months</b>	<b>24 months</b>
N	133	163	161	175
Mean (degrees)	4.9	6.0	7.0	7.4
Standard deviation (degrees)	3.89	4.56	4.92	5.24
Median (degrees)	4.4	5.2	6.3	6.9
Range, min-max (degrees)	0-19	0-20	0-20	0-22

Normal segmental range of motion is defined as up to 10 degrees of motion measured on lateral flexion-extension films.

### Mean Vertebral Flexion-Extension ROM (degrees)



Normal lumbar segmental range of motion has been documented in the literature. In Percy and Shepherd (Percy M, Portek I, Shepherd J: Three-dimensional x-ray analysis of normal movement in the lumbar spine. *Spine*, 9(3): 294-297, 1984), the radiographically measured range of motion of the L<sub>4</sub>L<sub>5</sub> motion segment was 13 degrees of flexion and 2 degrees of extension, with a 16 degree flexion-extension arc (s.d. = 4 degrees). At the L<sub>5</sub>S<sub>1</sub> motion segment, the range of motion was 9 degrees of flexion and 5 degrees of extension, with a 14 degree flexion-extension arc (s.d. = 5 degrees). Therefore, the mean range of motion found in this investigation (4.9 at 3 months up to 7.4 degrees at 24 months) was within the normal range of motion, and the patients at the extreme ROM (up to a mean of 22 degrees) are still within 2 standard deviations of the mean. Thus, the Charité patients did achieve near-normal segmental motion at the operated segments.

The design characteristics of the device allow for 24 degrees of flexion, 32 degrees of extension, 32 degrees of lateral bending, and 360 degrees of axial rotation. Thus, the clinically demonstrated motion is within the design parameters for the device.

The lateral bending and axial rotational range of motion were not reported for this investigation. The normal range of motion reported in Percy and Tibrewal (Percy MJ and Tibrewal SB: Axial rotation and lateral bending in the normal lumbar spine measured by three-dimensional radiography. *Spine*, 9(6): 582-587, 1984) at the L<sub>4</sub>L<sub>5</sub> motion segment was found to be 3 degrees of axial rotation (range 1-5 degrees), and 6 degrees of lateral bending (range 1-9 degrees). For the L<sub>5</sub>S<sub>1</sub> motion segment, the normal range of motion was 2 degrees of axial rotation (range 0-3 degrees), and 3 degrees of lateral bending (range 1-6 degrees). Because these motions were not measured in this IDE study, no conclusions about the device's ability to restore normal lateral bending and rotational ranges of motion can be made.

#### DEVICE MIGRATION (Tables 35.1)

There were no device migrations reported for the BAK group. At 3, 6, 12, and 24 months, there were 2 (1%), 1 (1%), 2 (1%), and 3 (2%) migrations >3mm in the Charité group.

#### PSEUDARTHROSIS AND RADIOLUCENCIES

In the BAK group, there were 2 (3 %) patients with a pseudarthrosis at 6 months, 2 (3%) at 12 months, and 4 (5%) at 24 months (Table 35.1). In the Charité group, a radiolucency was identified in 1 (1%) patient at 12 months and 2 (1%) patients at 24 months; longitudinal ossifications were identified in 1 (1%), 3 (2%), 6 (4%), and 11 (6%) patients at 6 weeks, 6 months, 12 months and 24 months, respectively (Tables 35.1 and 36.1).

#### WORK STATUS (Table 37.1)

For both groups, there were decreases in the number of patients on short-term disability compared to baseline. At baseline, there were 15 (8%) patients in the Charité group compared to 8 (6%) patients in the BAK group on short-term disability. At 12 months, there were 1 (1%) and 1 (1%) patient, respectively, and at 24 months there were 1 (1%) and 0 patients, respectively, on short-term disability.

#### SUBJECT SATISFACTION (Table 38.1)

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Subject satisfaction was higher for the Charité group patients than the BAK patients. At 24 months, the difference was significant (p=0.0092).

<b>Patient Satisfaction</b>				
	12 months		24 months	
	Charité Group	BAK Group	Charité Group	BAK Group
N	182	85	182	85
Satisfied	118 (72%)	42 (59%)	129 (73%)	43 (55%)
Somewhat satisfied	33 (20%)	16 (23%)	27 (15%)	20 (26%)
Somewhat dissatisfied	8 (5%)	6 (8%)	17 (10%)	5 (6%)
Dissatisfied	6 (4%)	7 (10%)	4 (2%)	10 (13%)
Same treatment?				
Definitely YES	123 (74%)	42 (59%)	122 (69%)	40 (52%)
Probably YES	22 (13%)	12 (17%)	23 (13%)	10 (13%)
Not sure	14 (8%)	9 (13%)	21 (12%)	12 (16%)
Probably NOT	2 (1%)	3 (4%)	1 (1%)	5 (6%)
Definitely NOT	6 (4%)	5 (7%)	10 (6%)	10 (13%)

**?? Adverse Events**

The sponsor collected adverse event information on all randomized patients (“Safety Population”), and categorized them as follows: typical or unusual (Table 40.1-40.2); severe or life-threatening (Table 41.1-41.2); device-related or not device-related (Table 42.1-42.2); severe and device-related (Table 43.1-43.2); occurring within 2 days of surgery (Table 44.1-44.2); and by date of onset categories (Table 45.1-45.2).

<b>Adverse Events Table 39</b>				
	<b>Charité Group</b>		<b>BAK Group</b>	
	Patients	%	Patients	%
Patients enrolled	205		99	
<b>Patients with an adverse event</b>	<b>156</b>	<b>76.1</b>	<b>77</b>	<b>77.8</b>
Pain, back or lower extremity, total	107	52.5	52	52.5
Device-related	10	4.9	2	2.0
Not Device-related	97	47.3	50	50.5
Other	46	22.4	26	26.3
Neurological, total	34	16.6	17	17.2
Device-related	3	1.5	0	0
Not Device-related	31	15.1	17	17.2
Pain (other), total	27	13.2	9	9.1
Device-related	0	0	0	0
<b>Not Device-related</b>	<b>27</b>	<b>13.2</b>	<b>9</b>	<b>9.1</b>
Infection, total	25	12.2	6	6.1
Device-related	1	1	0	0
Not Device-related	14	11.7	6	6.1
Approach problems (abdominal)	18	8.8	8	8.1
Fusion treatment related	0	0	26	26.3
Device-related	0	0	1	1.0
Not Device-related	0	0	25	25.3
DDD progression, natural history, total	6	2.9	4	4.0
Device-related	0	0	1	1.0
Not Device-related	6	2.9	3	3.0
Prosthesis related, total	8	3.9	1	1.0
Device-related	2	1.0	0	0
Not Device-related	6	2.9	1	1.0



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Additional surgery, Index level	10	4.9	8	8.1
Device-related	5	2.4	1	1.0
Not Device-related	4	2.0	8	8.1
Additional surgery, other than index level	3	1.5	3	3.0
Intraoperative complications	2	1.0	3	3.0
Abnormal bone formation	2	1.0	0	0

**Severe or Life-Threatening Adverse Events:**

There were 30 (15%) severe or life-threatening adverse events in the Charité group, compared to 9 (9%) in the BAK group.

<b>Severe or Life-Threatening Adverse Events</b>				
<b>Table 41.2</b>				
	<b>Charité Group</b>		<b>BAK Group</b>	
	Patients	%	Patients	%
Patients enrolled	205		99	
<b>Patients with severe or life-threatening AE</b>	<b>30</b>	<b>15</b>	<b>9</b>	<b>9</b>
Pain (back or lower extremities)	10	4.9	5	5.1
Other, total	11	5.4	3	3.0
Other, cardiovascular	0	0	1	1.0
Infection	3	1.5	2	2.0
Additional surgery, index level, removal	4	2.0	0	0
Additional surgery, index level, delayed fusion	1	<1.0	0	0
Additional surgery, index level, reoperation	1	<1.0	0	0
Approach problems (abdominal)	2	<1.0	1	1.0
Approach problems, hernia	1	<1.0	0	0
Approach problems, retrograde ejaculation	1	<1.0	1	1.0
Additional surgery, unrelated to index level	1	<1.0	1	1.0
Neurological, nerve root injury	1	<1.0	0	0

**Device-Related Adverse Events:**

There were 15 (7.3%) device-related adverse events in the Charité group, compared to 4 (4.0%) in the BAK group. Most of these adverse events were “device-related” pain (10, or 4.9%, in the Charité group v. 2, or 2%, in the BAK group). Despite the higher incidence of pain due to the Charité device, the Charité group still had 74% Pain VAS successes compared to 62% in the BAK group (p=0.0759). Other device-related adverse events were <1% in both groups (Charité: nerve root injury, subsidence, displacement, removal; BAK: nonunion, degeneration at another level).

<b>Device-Related Adverse Events</b>				
<b>Table 42.2</b>				
	<b>Charité Group</b>		<b>BAK Group</b>	
	Patients	%	Patients	%
Patients enrolled	205		99	
<b>Device-related adverse events</b>	<b>15</b>	<b>7.3</b>	<b>4</b>	<b>4.0</b>
Pain, back	5	2.4	1	1.0
Pain, back and lower extremities	5	2.4	1	1.0
Pain, lower extremities	2	<1.0	0	0
Nerve root injury	1	<1.0	0	0
Collapse, subsidence	1	<1.0	0	0
Implant displacement	1	<1.0	0	0
Removal of prosthesis	1	<1.0	0	0

**Adverse Events Onset:**

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The time course of adverse events is similar for the Charité and the BAK groups, although there is a slightly greater incidence of adverse events after 210 days in the BAK group (additional surgeries at the index level).

**Major Adverse Events:**

Major adverse events, as defined in the success/failure criteria as major vessel injury or blood loss (>1500cc), neurological damage, or nerve root injury, were infrequent. There were 2 (<1%) in the Charité group and 1 (1%) in the BAK group. These were neurological deterioration (1) and major vessel injury (1), and a major vessel injury (1), respectively, for the two groups.

**Device Failures:**

Device failures were defined as a reoperation, revision, removal, or supplemental fixation of the device. There were 10 patients (4.9%) in the Charité group and 8 patients (8.1%) in the BAK group with device failures.

<b>Device Failures Table 34</b>				
	<b>Charité Group</b>		<b>BAK Group</b>	
	Patients	%	Patients	%
Patients enrolled	205		99	
<b>Device failures</b>	<b>10</b>	<b>4.9</b>	<b>8</b>	<b>8.1</b>
Reoperation	0	0	1	1.0
Revision	0	0	1	1.0
Removal	2	<1.0	0	0
Supplemental fixation	8	3.9	6	6.1

The reasons for each device failure and the treatment given are tabulated below:

<b>Charité Group Device Failures Narrative Summaries, Section 8.4.6.5, pp.59-70</b>				
<b>Patient</b>	<b>Level</b>	<b>Reason for Failure</b>	<b>Problem</b>	<b>Treatment</b>
01045	L <sub>5</sub> S <sub>1</sub>	Supplemental	SI joint pain	Fusion
01078	L <sub>4</sub> L <sub>5</sub>	Supplemental	Unresolved pain	Fusion
03016	L <sub>5</sub> S <sub>1</sub>	Supplemental	Pain, spondylolisthesis	Fusion
03023	L <sub>5</sub> S <sub>1</sub>	Removal	Nerve root injury	Removal, fusion
05012	L <sub>5</sub> S <sub>1</sub>	Supplemental	Spondylolysis	Fusion
09014	L <sub>4</sub> L <sub>5</sub>	Supplemental	Pain	Fusion
09022	L <sub>4</sub> L <sub>5</sub>	Removal	Pain	Removal
10013	L <sub>4</sub> L <sub>5</sub>	Supplemental	Pain	Fusion
13008	L <sub>4</sub> L <sub>5</sub>	Supplemental	Pain	Fusion
13012	L <sub>5</sub> S <sub>1</sub>	Supplemental	Pain	Fusion

"Supplemental" = patient required fusion at the index level.

**Deaths:**

There was one death in the Charité group from an apparent recreational drug overdose before the 6-week follow-up evaluation. This was unrelated to the device and procedure.

**Device Replacements:**

The sponsor provided a description of 5 patients who required Charité implants replacement during the index procedure, i.e., without an inciting adverse event (Section 8.7, p.89). In all cases, the implant was recognized by the surgeon that the implant was either the wrong size or not in the ideal position. There were no post-operative complications.

**Training Cases Results**

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Each investigative site was required to enroll their first 5 patients as training cases. They all received the Charité Artificial Disc. There were 71 patients enrolled as training cases at 15 investigational sites. These patients were not included in the ITT analysis by protocol.

Training Cases	
N	71
Early discontinuation	7 (10%)
Completed study	60 (84.5%)

The demographics were similar to the randomized group: 30 (42%) were men, 41 (58%) women, mean age 38.5 years. The surgery was performed at the L<sub>4</sub>L<sub>5</sub> level in 19 patients, and at the L<sub>5</sub>S<sub>1</sub> level in 52 patients.

There were 7 early withdrawals: 3 voluntarily withdrew; 2 were non-compliant; 1 refused follow-up; 1 failed because of pain and the device was removed.

**Effectiveness:**

The effectiveness appeared to be comparable to the Randomized patients. All of the effectiveness parameters were either better or comparable to the Randomized group scores, including the improvement in Oswestry scores, lack of neurological deterioration, improvement of the Pain VAS, improvement in the SF-36, and radiographic assessments (lack of loss of disc height, lack of migration). In addition, the work status improved from 13% on short-term disability to 3% at 12 months and 2% at 24 months. Patient satisfaction was good: 81% at 12 months and 83% at 24 months (compared to 71% and 73%, respectively, for the Randomized patients).

**Safety:**

There were higher early (within the first 2 days of surgery) adverse events in the Training Cases group (33 patients, or 46.5%) than in the Randomized group (58 patients, or 28.3%). The rates at all other time periods are similar between groups. There were more device-related adverse events in the Training Cases group (8 events, or 11.3%) than in the Randomized group (14 events, or 6.8%).

**Discussion:**

The Training Cases performed well despite having a higher complication rate. The higher early adverse event rate is not unexpected. The types and severity of the complications is not different from the Randomized group.

**Continued Access Cases Results**

The sponsor was allowed to continue to enroll up to a total of 615 continued access patients. They all received the Charité Artificial Disc. There were 71 patients enrolled as continued access cases who have completed the 12-month follow-up evaluation as of 9/03. These patients were not included in the ITT analysis by protocol.

The demographics were similar to the randomized group: 31 (44%) were men, 40 (56%) women, mean age 37.7 years. The surgery was performed at the L<sub>4</sub>L<sub>5</sub> level in 28 patients, and at the L<sub>5</sub>S<sub>1</sub> level in 43 patients.

There were 7 early withdrawals: 3 voluntarily withdrew; 2 were non-compliant; 1 refused follow-up; 1 failed because of pain and the device was removed.

**Effectiveness:**

The effectiveness appeared to be comparable to the Randomized patients. All of the effectiveness parameters were either better or comparable to the Randomized group scores, including the improvement in Oswestry scores, lack of neurological deterioration, improvement of the Pain VAS, and improvement in the SF-36. Patient satisfaction was good: 74% at 12 months (compared to 73% for the Randomized patients).

**Safety:**

The early adverse event rate in the Continued Access patient group was the lowest rate of all the groups: Continued Access 21%, Randomized group 28%, Training Cases 46%.

**Discussion:**

The Continued Access group performed comparably to the Randomized group in terms of effectiveness and early adverse events.

**VALIDITY OF THE BAK CONTROL GROUP**

The BAK Interbody Fusion System is a well-accepted treatment in the orthopedic community and is a reasonable comparison treatment. Because it was implanted via an anterior approach, it also minimized the approach-related variables. The demonstrated presence of segmental motion at the Charité Artificial Disc-implanted level contrasts well with the lack of motion at the BAK-fused level. Other variables, such as device migrations, replacements, removals, and reoperations, also make these treatments ideally suited as comparison products. Therefore, the study's control group treatment is a reasonable treatment for this clinical indication, and the results are comparable to known clinical studies for the same indication.

**OTHER CLINICAL INFORMATION**

The sponsor provided several other unpublished reports pertaining to the Charité Artificial Disc.

?? "French surgeon's report of an explant 9.5 years after insertion"

This is an analysis report of an explanted Charité Artificial Disc ("SB Charite III") removed 9.5 years after the original operation. The endplates were found to be in excellent condition—no scratches or other damage. The polyethylene core was fragmented into multiple pieces. Shear failure occurred between the superior and inferior hemispheres of the bi-concave portion.

?? "Explant from Australia"

Approximately 3 years after implantation, radiographs demonstrated metal-on-metal contact of the endplates, and radiographs demonstrate osteolysis. The surgeon was not able to remove the implant because of "friable and adherent blood vessels and blood loss." Biopsy showed PE debris.

**CLINICAL UTILITY** (Sections 8.8, 8.9, pp.98-100)

The sponsor provided a risk-benefit analysis of the clinical utility of the treatments in terms of safety and effectiveness, and emphasized that the Oswestry Disability Index and Pain VAS scores were significantly improved in the Charité Artificial Disc patients, and the Charité Artificial Disc preserves segmental motion.

**DISCUSSION**

There are some general concerns for this product. Although the Charité Artificial Disc was highly successful in relieving pain, there were a significant number of patients who did not obtain pain relief: 14% had no pain relief or had their pain worsen, and an additional 13% had only partial pain relief. The etiology of their unrelieved pain is not known. However, it is possible that despite having facet joint arthrosis as an exclusion criterion, the spinal motion segment is a three-joint entity, and facet joint degeneration is probably present at least to small degree in all patients with degenerative disc disease.

The facet joints are synovial joints, lined by hyaline cartilage and encased in a fibrous capsule. They degenerate in concert with the disc space. Their primary function is to protect the disc space from shear and rotational (torsion) forces. The normal facet joints guide the motion of the functional spinal unit in the sagittal plane, and limit motion rotation and bending. Their secondary role is to share a portion of the axial load when standing (0% when sitting). The lumbar facet joints bear up to 20% of the compressive loads, particularly in extension. When degenerative changes develop in the disc space, the facet joints share even more of the load. Facet joints also degenerate like knee joints, and form typical osteoarthritic pathologic changes. Degenerated facet joints can be painful. Free nerve endings are also present in the fibrous capsule of the facet joint. Pain can originate from the three-joint complex of the disc and the facet joints. Painful osteoarthritic degeneration of the facet joints was called the "facet syndrome" in 1933 (Ghormley). It is usually a fairly constant mechanical back pain and is almost always bilateral. Pure facet syndrome pain is off the midline, tends to be proximal over the sacroiliac joints, and is rarely referred to the thighs. In contrast, pain from isolated degenerative discs tends to be central.

This may be a source of continued pain in patients unsuccessfully treated with disc replacement surgery. Whether the disc replacement is able to unload the facet joints sufficiently to effectively treat this region is unknown. This may be an unaddressed problem of disc replacement surgery.