Comparison of the Clinical Outcome Results for the Spinal Kinetics M6®-C Artificial Cervical Disc to the Published US Investigational Device Exemption (IDE) Results for the PRESTIGE® ST, BRYAN® and ProDisc™-C Artificial Cervical Discs

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Abstract

**Purpose:** The purpose of this paper is to report the combined 2-year clinical and radiographic results of the M6-C clinical studies and compare those results to those presented in the published US Investigational Device Exemption (IDE) pivotal study publications for the 3 artificial cervical discs approved for use in the United States.

**Methods:** Major components of the study design for the M6-C German Registry and US IDE pilot study were similar which allowed combination of the data to create the M6-C study group. Ninety nine patients were enrolled in the combined cohort with 64 patients completing the 24-month follow-up. The M6-C results were compared to those obtained from published literature and from the Summary of Safety and Effectiveness for the 3 artificial cervical discs approved for use in the United States. The 3 reference IDE protocols had similar study designs and were approved by the Food and Drug Administration (FDA).

**Results:** Baseline characteristics and baseline clinical outcomes measures for the M6-C study group were comparable to those of the PRESTIGE ST, BRYAN and ProDisc-C. The M6-C and reference device patient groups all showed significant improvement at 24 months compared to baseline for all of the clinical outcomes measured. The rates of device related Adverse Events requiring re-operation were low for the M6-C and reference study groups.

**Conclusion:** Comparison of the combined results for the M6-C German Registry and US IDE Pilot Study to the results from published data for the PRESTIGE ST, BRYAN and ProDisc-C through 24-month follow-up indicated general equivalence in all categories of safety and effectiveness for the M6-C compared to the 3 reference devices.

Introduction

Cervical radiculopathy describes a group of symptoms and signs related to dysfunction or disease of the cervical spinal nerve root(s). Characteristically, there is pain in the neck and in a radicular distribution in one or both upper extremities occurring in episodes often lasting several weeks, frequently accompanied by varying degrees of other motor, reflex and sensory changes. Arm pain is the most prevalent symptom. Approximately 25% of patients with symptomatic cervical radiculopathy undergo surgery within 3 months of diagnosis, typically for the combination of radicular pain, sensory loss and muscle weakness. Cervical radiculopathy is commonly caused by foraminal encroachment of the spinal nerve (in up to 75% of the cases) or to herniation of the nucleus pulposus (up to 25% of cases). Foraminal encroachment may be due to a combination of factors such as decreased disc height and cervical spondylosis. Surgery may be an effective solution for certain patient populations suffering from intractable cervical radiculopathy. Indications for surgery depend on
whether there is evidence of radiculopathy or signs of concomitant spinal cord impairment that could lead to irreversible neurologic deficits.\textsuperscript{1,2}

In the absence of myelopathy, surgery for cervical radiculopathy is typically recommended when the following are present: cervical root compression confirmed by MRI or CT myelography; signs and symptoms of cervical root-related dysfunction, pain or both; and 6 to 12 weeks of failed conservative management or exhibiting a progressive motor deficit.\textsuperscript{2} Surgery is also recommended when moderate to severe myelopathy is clinically confirmed.\textsuperscript{3,4}

Decompression followed by anterior cervical fusion is a well-accepted surgical procedure.\textsuperscript{4} However, a long term follow-up study in Belgium showed that as many as 92\% of patients with an anterior cervical interbody fusion had progressive degeneration in adjacent segments demonstrated by radiologic examination.\textsuperscript{5} Other long term studies of cervical fusion have shown that approximately 25\% of patients will have progressive degenerative symptoms within 10 years.\textsuperscript{4,6}

This etiology is likely related to biomechanical alterations imposed on the adjacent segments by the fusion.\textsuperscript{7,8} Artificial disc replacements were developed in an attempt to improve on these results by preserving motion.\textsuperscript{2,4} Advantages of disc replacement not only include preventing adjacent segment degeneration, but also maintaining cervical intervertebral motion that helps avoid complications related to fusion and allow earlier return to normal activities.\textsuperscript{4,9,10}

Three artificial cervical discs have been approved for use in the United States and a number of additional cervical discs are under investigation according to Investigational Device Exemption (IDE) protocols approved by the US Food and Drug Administration (FDA). The cervical discs approved for use in the US are the PRESTIGE ST Cervical Disc System (Medtronic Sofamor Danek, Memphis, TN, USA); the ProDisc-C (Synthes Spine, West Chester, PA, USA); and the BRYAN Cervical Disc System (Medtronic Sofamor Danek, Memphis, TN, USA). In addition to the 3 US approved cervical discs, numerous other cervical discs carry the CE mark and are available for use outside the United States (OUS).

There are literally hundreds of publications referring to the clinical use of artificial cervical discs, but only the 3 US FDA approved cervical discs have references to full data sets for FDA, IDE pivotal studies.

The Spinal Kinetics M6-C is an artificial cervical disc being investigated under an approved IDE in the United States and is among those cervical discs which carry the CE mark and are available for use OUS. The M6-C device has been studied clinically under 2 protocols, the US IDE Pilot Study and the German Patient Registry.

The purpose of this paper is to report the combined 2-year clinical and radiographic results of the primary M6-C clinical studies and compare those results to the data presented in the published US IDE pivotal study publications for the PRESTIGE ST,\textsuperscript{11} ProDisc-C,\textsuperscript{12} and BRYAN\textsuperscript{13} artificial cervical discs. In addition to the peer reviewed publications, reference to the Summary of Safety and Effectiveness (SSE)\textsuperscript{14-16} available on the US FDA website for each of the approved cervical discs was also used for some data points that were not presented in the respective publications.

Materials and Methods

\textbf{M6-C Study Descriptions}

\textbf{US IDE M6-C Feasibility Study:} The US IDE Feasibility Study for the M6-C Cervical Disc was a multi-center, single arm, prospective study to establish safety and effectiveness of the Spinal Kinetics M6-C artificial disc. FDA and Institutional Review Board (IRB) approvals were attained prior to patient enrollment. Between February and June 2008, 30 patients signed an IRB-approved informed consent and were enrolled into the study at 3 participating investigational sites across the United States.

\textbf{German M6-C Patient Registry:} The German Patient Registry for the Spinal Kinetics M6-C Cervical Disc was a multi-center, single arm, prospective post-market study to assess safety. The German Registry study was not a regulated study, but it was designed to provide more complete data than a typical post-market registry. The study was performed under Ethics Committee approval and required patient informed consent. Enrollment was initiated in July 2007 with the final patient entered in February 2008. Six clinical sites enrolled a total of 69 patients.

Protocols for both the US IDE Feasibility Study and the German Patient Registry contained inclusion/exclusion criteria based on the Instructions for Use (IFU) of the M6-C device. Skeletally mature patients with
symptomatic cervical radiculopathy and no myelopathy at 1 or 2 levels between C3 and C7 who had failed 6 weeks of conservative therapy (waived for patients with progressive neurological deficits or with severe pain requiring urgent surgical treatment) were included in the studies; patients that had advanced degenerative changes, as evidenced by extreme loss of disc height or extreme kyphosis or subluxation >3mm, and had used tobacco and NSAIDs 2-4 weeks prior to enrollment were excluded.

The primary selection criteria were identical for both the US IDE and the German cohorts, but the US IDE required all patients report neck disability greater than 40% as measured by the Neck Disability Index (NDI) and pain VAS of at least 4 on a 10 point scale.

**M6-C Clinical Outcomes:** Patients were evaluated pre-operatively and post-operatively according to specific criteria and to a follow-up schedule indicated in the respective protocol. In the US IDE Feasibility Study, follow-up was performed at 6 weeks and at 3, 6, 12 and 24 months post-operatively. In the German Patient Registry, follow-up was performed at 3, 12 and 24 months post-operatively. For both studies, the clinical evaluation at each visit included a subjective assessment of current neck related symptoms, upper extremity neurological examination, and self-assessment questionnaires including the Neck Disability Index (NDI)\(^1\), neck and arm pain visual Analogue Scales (VAS) and the SF-36 Health Survey.\(^2\) Device safety information was also collected on Adverse Events including any device failure such as implant/fiber breakage, sheath dislodgement, subsidence, migration or expulsion requiring additional surgical intervention.

**M6-C Radiographic Outcomes:** Standard cervical spine x-rays were performed pre and post-operatively. In the US IDE Feasibility Study, x-rays performed at each visit included neutral anterior-posterior (AP), neutral lateral, flexion-extension (F/E), and right and left lateral bending. For the M6-C German Patient Registry, a full series of x-rays were obtained by the investigators for some patients; however the investigators were permitted to adhere to their standard of care x-ray protocol specific for each site. At times, and in an effort to minimize radiation exposure, the standard of care x-ray protocol did not include a full series of images. Qualitative outcomes, such as osteophytes and radiolucency, and quantitative outcomes, such as intervertebral motion and disc height, were assessed prior to combining the two M6-C cohorts by a core laboratory (Medical Metrics, Inc., Houston, TX). Data for US and German M6-C cohorts and for the one and two-level disc replacements were pooled with respect to osteophytes because there was no evidence of any difference. Intervertebral motion was evaluated from flexion/extension by measuring: angular motion in degrees, translational motion in mm, the Center of Rotation (COR) in mm and the Range of Motion (ROM) in degrees. Longitudinal change in disc height was also reported.

In addition to the quantitative assessments performed, each study determined individual patient radiographic success based on the Intervertebral Rotation or Range of Motion (ROM) at the index level.

**PRESTIGE ST Study Description**\(^11,14\)

**PRESTIGE ST US IDE Pivotal Study:** This was a prospective randomized controlled study conducted under an FDA-approved IDE with a primary goal of assessing the safety and effectiveness of the PRESTIGE ST Cervical Disc System (Medtronic Sofamor Danek).\(^11\) Institutional Review Board approval was granted prior to patient enrollment in the study. Between October 2002 and August 2004, 541 subjects were enrolled, and treated at 32 investigational sites within the US. The patients were randomized 1:1 to receive the PRESTIGE ST Cervical Disc System prosthesis or the control treatment which was an “interbody fusion using a cortical ring allograft spacers and an ATLANTIS Cervical Plate System (Medtronic Sofamor Danek) for supplemental fixation”.\(^11\)

Adult patients with symptomatic single level degenerative disc disease (DDD) between C3 and C7, intractable radiculopathy, myelopathy, or both were included in this study. All patients had preoperative NDI scores greater or equal to 30 and pre-operative neck pain scores greater or equal to 20. Patients included in this study had unsuccessful conservative treatment for at least 6 weeks. Subjects with progressive neurological worsening had treatment performed in fewer than 6 weeks. All patients were diagnosed with single-level cervical disc disease as evidenced by pre-operative radiographic studies.
PRESTIGE ST Clinical Outcomes: Data were collected preoperatively, intra-operatively, and at routine postoperative intervals of 1.5, 3, 6, 12, and 24 months. Peri-operative procedure details and Adverse Events were recorded. Primary and secondary outcome measures that were used to evaluate the patient’s condition pre and post-operatively included the NDI, neck and arm pain Numeric Rating Scales (NRS), the SF-36 Health Survey, neurological status and work status.

PRESTIGE ST Radiographic Outcomes: Neutral AP, neutral lateral, and F/E radiographs were obtained pre and intra-operatively and at 1.5, 3, 6, 12 and 24 months post-operatively to determine functional spinal unit height. Radiographic studies were assessed by two independent radiologists at specified time points. Functional spinal unit height was derived from the radiographs and sagittal-plane angular motion was determined using Cobb criteria.

BRYAN Study Description

BRYAN US IDE Pivotal Study: Patients eligible for participation presented with radiculopathy or myelopathy caused by single-level cervical disc disease due to disc herniation that had failed at least 6 weeks of conservative treatment (waived for those cases requiring immediate treatment). The study was approved by an Institutional Review Board and all patients had signed an informed consent prior to participation. Between May 2002 and October 2008, a total of 463 patients were enrolled and treated at 30 investigational sites. Patients were randomized to either receive treatment with the investigation device, the BRYAN Cervical Disc, or to undergo fusion with anterior cervical plating system and a bone allograft (ACDF). The ACDF procedure consisted of using a commercially available allograft in addition to ATLANTIS™ Cervical Plate System (Medtronic Sofamor Danek). Patients in the investigational group were treated with a 2-week postoperative course of a non-steroidal anti-inflammatory drug.

BRYAN Clinical Outcomes: Patients were evaluated preoperatively, intraoperatively, at 1.5, 3, 6, 12, and 24 months postoperatively. Clinical outcomes evaluated were neck disability index (NDI), neurological status, neck/arm pain using NRS and the SF-36 Health Survey. Adverse Events were collected and rates were reported.

BRYAN Radiographic Outcomes: Neutral AP, lateral and F/E radiographs were obtained and evaluated at the protocol defined intervals. Radiographic outcomes were assessed for functional spinal unit height and evaluation of angular motion using the Cobb technique for investigational patients and for fusion for the control group. Radiographic assessment was done by two independent radiologists.

ProDisc-C Study Description

ProDisc-C US IDE Pivotal Study: Between August 2003 and October 2004, 209 patients enrolled at 13 investigational sites across the United States and were randomized to either receive an interventional treatment, total disc replacement with ProDisc-C, or an anterior cervical discectomy and fusion. Institutional Review Board approval was obtained at each site and all enrolled patients had symptomatic cervical disc disease (SCDD) between C3 and C7 and were unresponsive to at least six weeks of conservative treatment with an NDI score greater or equal than 15/50 (30%).

ProDisc-C Clinical Outcomes: All patients’ clinical outcomes were evaluated preoperatively, at 1.5, 3, 6, 12, 18, and 24 months postoperatively. Clinical outcomes included physical and neurological examination, the NDI, SF-36 Health Survey, neck/arm pain VAS, subject satisfaction and employment status. Adverse Events and other complications were also collected during the study.

ProDisc-C Radiographic Outcomes: Radiographic studies included AP, neutral lateral, F/E, and right and left lateral bending films and were used to evaluate Adverse Events. The radiographs were reviewed by an independent radiologist and radiographic analyses were performed by a core laboratory (Medical Metrics Inc. Houston, TX). Additional quantitative radiology results such as Range of Motion (ROM) and disc height were reported.

M6-C Device Description

The M6-C artificial cervical disc (Spinal Kinetics, Sunnyvale, CA) is an advanced generation artificial disc designed to replicate the anatomic, physiologic and biomechanical characteristics of the native disc. The polymer core of the disc is composed of a polycarbonate urethane (PCU) that is surrounded by an ultra high molecular weight polyethylene (UHMWPE)
woven fiber construct and is sandwiched between two titanium alloy endplates to form the cervical disc prosthesis (Figure 1). The compressible polymer core is designed to simulate the stiffness and function of the nucleus, and the fibers are designed to simulate the function of the annulus. The fiber annulus is an assembly of high tensile strength, UHMWPE fibers wound in multiple redundant layers around the polymer nucleus, providing progressive resistance to motion. This unique design enables the M6-C artificial disc to have all six degrees of freedom including axial compression with independent angular motions in flexion-extension, lateral bending and axial rotation along with independent translations along the three anatomic axes.

The prosthetic disc also has a polymer sheath designed to minimize tissue ingrowth and wear debris migration. The endplates are attached to the vertebral body via three low profile keels on the superior and inferior surfaces. The keels provide acute fixation to the superior and inferior vertebral bodies within the intervertebral space. The endplates and keels are coated with titanium plasma spray to promote bone-contact surface area and osseointegration.

Figure 1: The M6-C artificial cervical disc is comprised of a compressible polymer core, polyethylene fiber annulus, titanium endplates and polymer sheath.

The surgical implantation of the M6-C requires specific instruments including: a Trial implant to determine the appropriate size and position of the implant; a Chisel to create keel tracks into the superior and inferior vertebral bodies; and an implant Inserter to place the disc into the desired position and to aid in correct placement within the intervertebral space.

The instruments are composed of surgical stainless steel and are intended to be reusable.

**PRESTIGE ST Device Description**

The PRESTIGE ST Cervical Disc System is a device made of two articulating stainless-steel plates with a ball-in-trough mechanism (Figure 2). Two bone screws are used to affix the device to the anterior vertebral bodies. The PRESTIGE Cervical Disc System is available in various sizes permitting adaptability to individual patient anatomy.\(^{11,14}\)

Figure 2: The PRESTIGE ST Cervical Disc System is a stainless steel device with a ball-in-trough articulation

**BRYAN Device Description**\(^{16}\)

The BRYAN Cervical Disc is made of 5 components which include a polycarbonate polyurethane (PCU) nucleus, titanium alloy shells and seal plugs, a polyether polyurethane sheath and titanium retaining wires (Figure 3).

The PCU nucleus is mounted between the two titanium alloy shells. These shells have inward facing posts that do not contact the nucleus but fit into flared holes and allow controlled range of motion. The beaded, vacuum-sintered titanium coating on the outer sides of the shells promotes bone growth on the implant. The shells posts have holes through which saline is injected and retained by screwing the titanium alloy seal plugs into the shells prior to implantation. The polyurethane sheath allows containment of the saline solution, restricts tissue growth into the device and is held onto the shells via the two titanium retaining wires.

Figure 3: The BRYAN Cervical Disc system.

**ProDisc-C Device Description**\(^{12,15}\)

The ProDisc-C artificial disc follows the ball-and-socket design principle. It consists of two endplates with midline keels to allow fixation to the inferior and superior vertebral bodies (Figure 4). The endplates are made using cobalt chromium molybdenum (CoCrMo) alloy and coated with titanium plasma spray to promote bone ongrowth. An ultra high–molecular weight polyethylene (UHMWPE) convex dome inlay is snap-locked into the inferior plate and articulates with the superior plate concave bearing surface. The disc is
available in various sizes to accommodate different vertebral endplate sizes.

Figure 4: The ProDisc-C total disc replacement comprises two cobalt chromium molybdenum alloy endplates with central keels and an ultra high-molecular weight polyethylene convex inlay.

**M6-C Surgical Technique**

**Positioning, Approach, and Decompression:** The patient is positioned supine with the cervical spine aligned without rotation and in a neutral position to match the standing lateral X-ray. Extension or flexion of the cervical spine is avoided. A soft roll or similar support is placed under the neck and other stabilizing techniques such as securing tape across the forehead may be used as desired to prevent unwanted movement during surgery. Access to the disc space is accomplished via standard anterior approach following radiographic confirmation of the index level. The correct disc space is reconfirmed, and, at the choice of the surgeon, retainer pins are placed in the vertebral bodies, in the midline and parallel to the endplates. A discectomy is performed to the lateral annulus and to the posterior longitudinal ligament. A complete bilateral decompression is performed.

**M6-C Disc Space Preparation and Implant Procedure:** The Intervertebral Distractor is inserted to the posterior border of the disc space under fluoroscopic control. A posterior release and restoration of disc space height is performed, taking care not to over-distract. The posterior longitudinal ligament may be resected at the surgeon’s discretion. The vertebral endplates are prepared by removing cartilaginous material, taking care to preserve the cortical bone. If necessary, anterior and posterior osteophytes may be removed. The desired disc space height may be maintained via external retention. The Footprint Template is placed against the vertebral endplates to determine the proper size Trial footprint. Endplate coverage from within 1mm of the anterior and posterior borders is desired. To accommodate the best coverage anterior-posterior, slight medial resection of the uncinates may be performed to allow correct fit of the footprint in the mediolateral aspect. Using the midline-placed pins and/or the medial uncinates as reference, the chosen height and footprint size Trial is placed into the disc space under fluoroscopic control. Using the Center Alignment Ports (CAP) of the Trial to insure the C-arm is on plane to the disc space, the Trial is advanced so that the posterior border of the Trial is oriented to within 1mm of the posterior vertebral endplates. The desired anterior position of the Trial and correct restored height is verified by fluoroscopy (Figure 5). Anteroposterior fluoroscopy is performed, again using CAP to orient the C-arm on plane to the disc space, to confirm midline orientation of the Trial. The fluoroscope is returned to the lateral position, oriented to the lateral CAP and locked. The Trial is removed and the corresponding size Chisel is oriented to the midline. Any external distraction is removed. The angle of the Chisel handle is aligned to the vertebral space and adjusted to medial-lateral plane by observation of the lateral CAP. Under fluoroscopic control the Chisel is advanced until the position of the posterior edge of the Chisel reaches the location previously obtained by the Trial. The Chisel is removed using the Slide Hammer. The disc space is irrigated and suctioned. The corresponding size M6-C is loaded onto the Inserter and the keels of the implant are oriented to the keel tracks in the vertebral endplates. The Inserter is advanced under fluoroscopic observation until the posterior edge of the M6-C reaches the position obtained by the Chisel (Figure 5).
Reference Devices Surgical Technique

Surgical Approach: There are basic similarities in the surgical techniques for these devices that are consistent with the M6-C surgical technique. The patient is positioned in the supine position and a standard anterior approach is required to access the disc space at the index level. Disc space access is followed by surgical decompression of the space in preparation for implantation of each device.11-16

Reference Devices Implant Procedure: The implant procedure for each reference device varies according to the design characteristics of the respective device. For each device, disc space preparation is followed by implantation of the device.11-16

Statistical Methods

The results of the statistical analyses of the M6-C studies are considered preliminary due to the small sample size. The outcomes for safety and preliminary effectiveness of M6-C were combined for the US and OUS cohorts. Published results for the three reference groups for approved similar devices were extracted and are provided for comparison of patient populations and outcome measures.

For the purpose of objectively confirming that the two M6-C groups are sufficiently similar such that they could be combined into a single population, baseline and operative characteristics were statistically summarized via frequency and percentage distributions (e.g., gender, vertebral level) and descriptive statistics (e.g., age) to characterize the two individual study groups and the combined study group. In addition to baseline and operative characteristics, these comparisons included preoperative values for NDI, neck and arm pain VAS, and SF-36 physical and mental components summary scores.

For all clinical effectiveness measurements, including the NDI, arm and neck pain VAS and SF-36 component scores, the quantitative change between baseline and 24 months was determined and the associated significance levels were computed using a two tailed paired t-test. Additionally, the proportion of study subjects that achieved the minimal clinically important difference in change in NDI score (success) of 15 percentage points, was computed. For neck and affected arm pain (the arm with the highest pain reported at baseline), and SF-36 measures of Physical Component Summary (PCS) and Mental Component Summary (MCS), any improvement from baseline was considered a success for the purpose of these analyses.

Surgical duration, amount of blood loss, and length of hospitalization were summarized with descriptive statistics.

Data was captured in two SAS systems validated for data entry and verification and later merged for statistical analysis. A smaller percentage of patients in the German cohort had 24 months data compared to the US group; as a result, the subjects in the German group that had completed 24-month follow-up was evaluated for indications of differences with the entire German group on all baseline and operative characteristics for evidence of selection bias.

All statistical analyses for the M6-C group data were performed using SAS version 7 (Cary, NC).

Results

Baseline Characteristics/Outcome Measurements

The 3 reference studies reported no statistically significant differences at baseline between their respective investigational and control groups in gender, age, height, weight, BMI \(^*\) (not provided in the PRESTIGE ST study) and nicotine use (p > 0.05; Table 1).14-16 These same characteristics are reported for the M6-C cohort in Table 1.

The average age, height and weight of the M6-C group was similar to those of the reference groups. A few notable distinctions in the M6-C group compared to the reference groups are that the sample size of the M6-C is smaller and percent male and percent nicotine users are higher for the M6-C. These distinctions, while noted, do not affect comparability to the reference studies. Clinical outcome measurements included the NDI, Neck and Arm Pain and the PCS and MCS components of the SF-36 Quality of Life test instrument.

The M6-C baseline clinical outcome measures were comparable to the baseline clinical outcome measures in the reference studies (Table 2). The baseline comparability of M6-C group to the reference study groups in regard to baseline pain, function and quality of life measures supports the justification for comparing

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\(^*\) BMI in BRYAN study was significantly different between investigational and control group with higher BMI in control group\(^13\)
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>M6-C</th>
<th>PRESTIGE</th>
<th>ACDF</th>
<th>BRYAN</th>
<th>ACDF</th>
<th>ProDisc-C</th>
<th>ACDF</th>
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<tr>
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<td>276</td>
<td>265</td>
<td>242</td>
<td>221</td>
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<td>Female n, (%)</td>
<td>27 (42.2)</td>
<td>148 (53.6)</td>
<td>143 (54.0)</td>
<td>132 (54.5)</td>
<td>108 (48.9)</td>
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<td>Male n, (%)</td>
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<td>Age (yr) mean ± sd</td>
<td>44.5 ± 8.1</td>
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<td>Wt. (lb) mean ± sd</td>
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<td>BMI mean ± sd</td>
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<td>26.6 ± 4.8*</td>
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<td>Nicotine Use n, (%)</td>
<td>29 (45.3)</td>
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<td>61 (25.5)</td>
<td>53 (24.0)</td>
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NR = Not Reported
* p-value=0.027

Table 2. Baseline Clinical Outcomes Measures

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<th>BRYAN</th>
<th>ACDF</th>
<th>ProDisc-C</th>
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<td>265</td>
<td>242</td>
<td>221</td>
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<td>NDI mean ± sd</td>
<td>55.3 ± 18.9</td>
<td>55.7 ± 14.8</td>
<td>56.4 ± 15.9</td>
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<td>50.2 ± 15.9</td>
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<td>Neck Pain VAS mean ± sd</td>
<td>69.8 ± 25.3</td>
<td>68.2 ± 22.7</td>
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<td>75.4 ± 19.9</td>
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<td>Arm Pain VAS mean ± sd</td>
<td>54.4  ± 35.2</td>
<td>59.1 ± 29.4</td>
<td>62.4 ± 28.5</td>
<td>71.2 ± 19.5</td>
<td>71.2 ± 25.1</td>
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<td>61 ±27</td>
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<tr>
<td>SF-36 PCS mean ± sd</td>
<td>32.6 ± 11.5</td>
<td>32.4 ± 12.1</td>
<td>32.7 ± 12.4</td>
<td>42.3 ± 12.5†</td>
<td>44.6 ± 11.6†</td>
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<td>SF-36 MCS mean ± sd</td>
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NR = Not Reported
†p-value=0.041

the post-operative clinical outcome measurements for the respective study groups.

Surgery Outcomes

The most common level of treatment in the M6-C cohort was C5/C6 and the second most common was C6/C7. In all 3 reference studies, those were also the most common levels of treatment in both the investigational group and the control group. Mean blood loss was 53.4 ml in the M6-C group, which was slightly less, but generally comparable to mean blood loss in the reference studies. Mean surgery time for the combined single and 2-level M6-C cases was 83.6 minutes which was slightly less than the surgery time for the investigational group in all of the reference studies. For single level M6-C cases, the mean surgery time was less at 71.1 minutes, which is on average 25% less time than the closest reference group. Length of hospital stay in the M6-C German Registry was greater (mean of 6.7 days) than that of the M6-C US IDE Feasibility group and the reference studies. The length of hospital stay in the M6-C US IDE group was on average 1.3 days, which is comparable to the length of stay in the US IDE reference studies (Table 3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>M6-C</th>
<th>PRESTIGE</th>
<th>ACDF</th>
<th>BRYAN</th>
<th>ACDF</th>
<th>ProDisc-C</th>
<th>ACDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated Level n, (%)</td>
<td>0 (0.0)</td>
<td>7 (2.5)</td>
<td>10 (3.8)</td>
<td>3 (1.2)</td>
<td>0 (0.0)</td>
<td>3 (2.9)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>C3/C4</td>
<td>9 (14.1)</td>
<td>14 (5.1)</td>
<td>15 (5.7)</td>
<td>12 (5.0)</td>
<td>17 (7.7)</td>
<td>10 (9.7)</td>
<td>6 (5.7)</td>
</tr>
<tr>
<td>C4/C5</td>
<td>45 (70.3)</td>
<td>142 (51.4)</td>
<td>149 (56.2)</td>
<td>140 (57.9)</td>
<td>110 (49.8)</td>
<td>58 (56.3)</td>
<td>61 (57.5)</td>
</tr>
<tr>
<td>C5/C6</td>
<td>28 (43.8)</td>
<td>113 (40.9)</td>
<td>91 (34.3)</td>
<td>87 (36.0)</td>
<td>94 (42.5)</td>
<td>32 (31.1)</td>
<td>38 (35.8)</td>
</tr>
<tr>
<td>Blood Loss (ml)</td>
<td>53.4</td>
<td>60.1</td>
<td>57.5</td>
<td>91.5</td>
<td>59.6</td>
<td>83.5</td>
<td>63.5</td>
</tr>
<tr>
<td>Surgery Time (minutes)</td>
<td>83.6</td>
<td>96</td>
<td>84</td>
<td>132</td>
<td>84</td>
<td>107.2</td>
<td>98.7</td>
</tr>
<tr>
<td>Hospital Stay (days)</td>
<td>1.3 ‡</td>
<td>1.1</td>
<td>1.0</td>
<td>1.1</td>
<td>1.0</td>
<td>1.4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

‡US IDE patients only
**M6-C 24 Month Follow-up Rates**

The follow-up rate at 24 months for the US IDE Feasibility Study was 93.3% (28/30). One would expect such a high compliance rate for an FDA regulated study. As noted in the methods section, the investigators in the German Registry were given some latitude to follow the patients according to the standard of care. Because a 24 month follow-up is not typically standard of care, the follow-up rate at 24 months for the German Registry was only 52.2% (36/69) resulting in an overall 24-month compliance rate of the combined cohort of 64.6% (64/99). Evidence of potential bias in the completed registry cohort was assessed, and baseline and surgery characteristics for those German patients that completed 24-months follow-up were compared to the entire German cohort.

The German groups were found to be similar for all baseline and surgical characteristics, confirming the validity of the final cohort.

**Clinical Outcomes at 24 Months**

**Neck Disability Index (NDI)**

All 3 of the reference studies showed a statistically significant improvement from their respective baselines in mean NDI for both the investigational and control groups at the 24 months follow-up visit (p<0.001). The M6-C group also showed significant improvement from baseline in mean NDI at 24 months (p<0.0001) and compared favorably with the reference study groups for degree of both neck pain (Figure 8) and arm pain at 24 months (Figure 9). Individual patient success at 24 months was recorded in the reference studies as at least a 15 point improvement from baseline. The success rates at 24 months ranged from 76.6% to 84.3% (Table 4).

**Neck and Arm Pain**

Neck and Arm pain was measured using either Visual Analogue (VAS) or Numeric Rating Scales (NRS). In the ProDisc-C study, the patients were also asked to score the frequency of pain, but frequency of pain was not recorded in the other studies and will not be compared. There was a significant decrease in mean pain scores for both neck and arm pain at 24 months for all studies. The M6-C group also showed significant improvement from baseline (p<0.0001) and was comparable to the reference study groups for degree of both neck pain (Figure 8) and arm pain at 24 months (Figure 9). Success rate for neck and arm pain was defined in the reference studies as a decrease in pain at the 24-month time point. The success rate for neck and arm pain in the M6-C group was 87.3 and 92.1% respectively, and was comparable to the success rates for the reference studies (Table 4).
Table 4. Clinical Outcomes at 24 Months

<table>
<thead>
<tr>
<th>Variable</th>
<th>M6-C</th>
<th>PRESTIGE</th>
<th>ACDF</th>
<th>BRYAN</th>
<th>ACDF</th>
<th>ProDisc-C</th>
<th>ACDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDI mean ± sd</td>
<td>21.1 ± 18.2</td>
<td>19.3 (NR)</td>
<td>22.4 (NR)</td>
<td>16.2 ± 20.5</td>
<td>30.6 ± 19.8</td>
<td>21.4 ± 20.2</td>
<td>20.5 ± 18.4</td>
</tr>
<tr>
<td>NDI Success (%)</td>
<td>76.6</td>
<td>80.8</td>
<td>80.8</td>
<td>84.3</td>
<td>75.7</td>
<td>79.8</td>
<td>78.3</td>
</tr>
<tr>
<td>Neck Pain VAS mean ± sd</td>
<td>21.5 ± 24.5</td>
<td>14 (NR)</td>
<td>15 (NR)</td>
<td>23.0 (NR)</td>
<td>30.3 (NR)</td>
<td>27 ± 26</td>
<td>26 ± 25</td>
</tr>
<tr>
<td>Neck Pain Success (%)</td>
<td>87.3</td>
<td>93.8</td>
<td>81.8</td>
<td>95.6</td>
<td>92.9</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Arm Pain VAS mean ± sd</td>
<td>19.3 ± 26.5</td>
<td>13 (NR)</td>
<td>14 (NR)</td>
<td>19.1 (NR)</td>
<td>21.5 (NR)</td>
<td>21 ± 27</td>
<td>19 ± 22</td>
</tr>
<tr>
<td>Arm Pain Success (%)</td>
<td>92.1</td>
<td>90.6</td>
<td>94.2</td>
<td>94.3</td>
<td>89.3</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>SF-36 PCS mean</td>
<td>47.5</td>
<td>44</td>
<td>43</td>
<td>47.9</td>
<td>46.3</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>SF-36 PCS Success (%)</td>
<td>85.9</td>
<td>85.8</td>
<td>85.7</td>
<td>85.5</td>
<td>90.6</td>
<td>80.8</td>
<td>74.4</td>
</tr>
<tr>
<td>SF-36 MCS mean</td>
<td>46.7</td>
<td>50</td>
<td>51</td>
<td>51.7</td>
<td>51.7</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>SF-36 MCS Success (%)</td>
<td>64.1</td>
<td>66.1</td>
<td>73.9</td>
<td>69.8</td>
<td>72.5</td>
<td>71.8</td>
<td>68.9</td>
</tr>
</tbody>
</table>

NR = Not Reported

The Physical Component Score (PCS) and Mental Component Score (MCS) are sub-scores of the SF-36 that were used to determine Quality of Life (QOL) status in all of the studies. The mean scores for the PCS and MCS were not available for the ProDisc-C study. The improvement in the mean PCS score from baseline to 24 months in the M6-C group was 14.9 points (p<0.0001) and the improvement in the mean MCS score was 4.0 points (p=0.029). The improvement in mean SF-36 PCS scores in the M6-C group is similar to that of the other reference studies. The improvement in mean SF-36 MCS scores was somewhat lower in the M6-C group (Figure 10). The percent success for SF-36 PCS and MCS scores was calculated (Table 4) and defined as the number of patients exhibiting any improvement in each score at follow-up compared to baseline.

Adverse Events

The incidence of Adverse Events in general was low for both the M6-C and reference study groups. For the purpose of this comparison, the focus is placed on the number of patients experiencing Adverse Events resulting in secondary surgical procedures at the index level. One patient (1.6%) in the M6-C study group required a secondary surgery to remove the device and convert to fusion. The rate of secondary surgical procedures at the index level for the M6-C group was comparable to the reported rate of secondary surgery for the reference study groups (Table 5).

Table 5. Secondary Surgery at the Index Level

<table>
<thead>
<tr>
<th>Variable</th>
<th>M6-C</th>
<th>PRESTIGE</th>
<th>BRYAN</th>
<th>ProDisc-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Surgery at the Index Level</td>
<td>1.6%</td>
<td>1.8%</td>
<td>2.5%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>
### Table 6. Radiographic Outcomes

#### Baseline Radiographic Outcomes:

<table>
<thead>
<tr>
<th>Variable</th>
<th>M6-C</th>
<th>PRESTIGE</th>
<th>BRYAN</th>
<th>ProDisc-C&lt;sup&gt;19&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervertebral Rotation (ROM) (°) mean ± sd</td>
<td>9.2 ± 4.5</td>
<td>7.6 (NR)</td>
<td>6.5 ± 3.4</td>
<td>8.4 ± 0.7</td>
</tr>
<tr>
<td>Translational Motion (mm) mean ± sd</td>
<td>1.0 ± 0.74</td>
<td>0.26 (NR)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lateral Bending (°) mean ± sd</td>
<td>6.2 ± 4.1</td>
<td>NR</td>
<td>NR</td>
<td>5.6 ± 0.5</td>
</tr>
<tr>
<td>Disc Height (mm) mean ± sd</td>
<td>3.7 ± 0.82</td>
<td>NR</td>
<td>NR</td>
<td>3.7 ± 0.2</td>
</tr>
</tbody>
</table>

#### 24 Month Radiographic Outcomes:

<table>
<thead>
<tr>
<th>Variable</th>
<th>M6-C</th>
<th>PRESTIGE</th>
<th>BRYAN</th>
<th>ProDisc-C&lt;sup&gt;19&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervertebral Rotation (ROM) (°) mean ± sd</td>
<td>6.8 ± 4.9</td>
<td>7.9 (NR)</td>
<td>8.1 ± 4.8</td>
<td>9.6 ± 0.8</td>
</tr>
<tr>
<td>Translational Motion (mm) mean ± sd</td>
<td>0.69 ± 0.56</td>
<td>0.28 (NR)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lateral bending (°) mean ± sd</td>
<td>5.1 ± 3.4</td>
<td>6.4 (NR)</td>
<td>NR</td>
<td>5.7 ± 0.5</td>
</tr>
<tr>
<td>Disc height (mm) mean ± sd</td>
<td>5.6 ± 0.98</td>
<td>NR</td>
<td>NR</td>
<td>5.5 ± 0.2</td>
</tr>
<tr>
<td>Bone bridging (%)</td>
<td>1.6</td>
<td>NR</td>
<td>NR</td>
<td>2.9</td>
</tr>
<tr>
<td>Radiographic Success (%)</td>
<td>74.7</td>
<td>72.6</td>
<td>79.6</td>
<td>84.4</td>
</tr>
</tbody>
</table>

NR = Not Reported

#### Radiographic Outcomes at 24 Months

Quantitative assessments were completed for the M6-C group and demonstrated comparable results to those of the reference study groups (Table 6). The height of the intervertebral disc space increased significantly by 24-month visit (p<0.0001).

#### Discussion

A randomized, controlled clinical study is the gold standard for comparison of various modalities of treatment for a defined medical condition. For artificial cervical discs, the defined medical condition is intractable cervical radiculopathy. There are a variety of reasons why a randomized study comparing the various artificial cervical discs may not be feasible. Should the study be performed in the US, or should it be performed internationally where there are more cervical discs available for use? It is not possible to compare to all of the approved discs, so which disc should be used for treatment in the control group? And possibly the most important reason why a randomized, controlled clinical study comparing 2 or more artificial cervical discs is not feasible is the cost of such a study in the present economic environment. Literature comparison is an alternative valid method to compare the results from multiple clinical studies. The PRESTIGE ST Cervical Disc System, the BRYAN Cervical Disc System and the ProDisc-C are all approved for use in the United States for the treatment of intractable cervical radiculopathy. US approval of the 3 artificial cervical discs was based on the results of US IDE pivotal studies. Each pivotal study has been published and demonstrated that the investigational device was a safe and effective surgical treatment for intractable cervical radiculopathy and that the investigational device was comparable to the standard of care control group, which in each instance was Anterior Cervical Discectomy and Fusion (ACDF). FDA approval to perform a US IDE pivotal for the M6-C device has been granted and initiation is pending. An M6-C US IDE Pilot Study and a post-market German Registry have been performed under very similar protocols, similar inclusion/exclusion criteria, and outcome measures and were performed under Institutional Review Board or Ethics Committees approvals, required patient informed consent and were monitored periodically. A noteworthy difference in the studies was the stipulation that the investigators in the Registry study were given some latitude to follow the patients according to their local standard of care practices. Baseline and operative characteristics of both cohorts were compared and confirmed to be similar permitting the creation of the M6-C study group comprised of the US IDE Feasibility and German Patient Registry cohorts. For this paper, the reference device publications chosen are the basis for
comparing the safety and effectiveness of the M6-C device to the US approved artificial cervical discs.

Due to the historical nature of these studies and the relatively small sample size of the M6-C cohort, it was not possible to do a statistically justified comparison of the M6-C results to that of the reference discs. Instead, a general comparison of the study outcomes was performed that included the Neck Disability Index, arm and neck pain scales, the SF-36 Quality of Life test instrument and safety. The results for the M6-C study group and the results obtained for both the investigational and control groups in the reference studies indicated general comparability in baseline characteristics, levels treated and outcomes at 24 months post-surgery. For other operative characteristics, the M6-C group showed better outcomes with regards to blood loss and surgery time compared to the reference groups, both potentially considered as positive attributes for the M6-C device. While the length of hospital stay for the German Patient Registry was significantly longer compared to the M6-C US IDE Feasibility group (6.7 vs. 1.3 days respectively) and the other US IDEs reference studies, it may be attributed to the difference in health care system rather than necessity. Although all of the referenced study IDE protocols required X-rays, very little quantitative radiology analysis is reported in the respective publications. Overall, radiographic outcomes for the M6-C device compared favorably to the reference devices. Additionally, the physiologic design of the M6-C device allows for a close to normal post-operative Center of Rotation, which should lead to less stress on posterior elements and adjacent levels in the post-operative time period. Medical Metrics concludes:

“The ability of the M6-C to support a COR that is below the disc in the sagittal plane but above the disc in the coronal plane suggests that it may support a helical axis of motion (HAM) consistent with true, 6-DOF kinematics”.

A small number of serious device related Adverse Events were observed for the M6-C device similar to the reference devices, and the percentage of patients requiring a reoperation at the index level closely compared to that of the reference groups. The studies included in this comparative analysis had various limitations: two of the 3 US IDE reference studies had large sample sizes and were randomized studies, but had limited radiographic outcomes which restricted any comparative analysis; the M6-C study was a prospective case series with a relatively small sample size; and a low follow-up rate for the German Registry cohort affected the overall combined M6-C cohort follow-up rates.

As is the case with other implantable devices, a longer term follow-up will be needed in order to ascertain longer term safety and effectiveness of the artificial disc beyond the 2-year follow-up.

Conclusion

The M6-C artificial cervical disc is an advanced generation artificial disc designed to replicate the anatomic, physiologic and biomechanical characteristics of the native disc. The results from a combined M6-C study group comprised of patients from a US IDE Feasibility Study and German Patient Registry indicate that the M6-C device is safe and effective through 2-year follow-up when used for the treatment of intractable cervical radiculopathy with results comparable to those obtained in US IDE studies for PRESTIGE ST, the BRYAN and the ProDisc-C artificial cervical discs.

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Medical Metrics, Inc., Houston, TX for radiographic analysis
References


