

# SUMMARY OF SAFETY AND EFFECTIVENESS (SSED)

## I. GENERAL INFORMATION

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Device Generic Name: Permanent drug-eluting pacemaker electrode

Device Trade Name: Medtronic Attain StarFix<sup>®</sup> Lead Model 4195

Applicant's Name and Address: Medtronic, Inc.  
8200 Coral Sea Street  
Mounds View, MN 55112-4391

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P060039

Date of Notice of Approval to Applicant: June 13, 2008

Expedited: Not applicable

## II. INDICATIONS FOR USE

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The Medtronic Attain StarFix Model 4195 steroid eluting, transvenous lead with deployable lobe fixation is intended for chronic pacing and sensing of the left ventricle via the cardiac vein, when used in conjunction with a compatible implantable pulse generator or implantable cardiac defibrillator.

## III. CONTRAINDICATIONS

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Coronary vasculature – This lead is contraindicated for patients with coronary venous vasculature that is inadequate for lead placement, as indicated by venogram.

Steroid use – Do not use in patients for whom a single dose of 30 µg (micrograms) of beclomethasone dipropionate (BDP) cannot be tolerated.

## VI. WARNINGS AND PRECAUTIONS

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The warnings and precautions can be found in the Attain StarFix Model 4195 lead labeling.

## V. PRODUCT DESCRIPTION

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The Attain StarFix Model 4195 lead is a device/drug combination product made up of two regulated components: a device (the Medtronic Attain StarFix lead) and a drug component (beclomethasone dipropionate). The characteristics of the Model 4195 appear in Table 1.

**Table 1: Design of Attain StarFix Model 4195 lead**

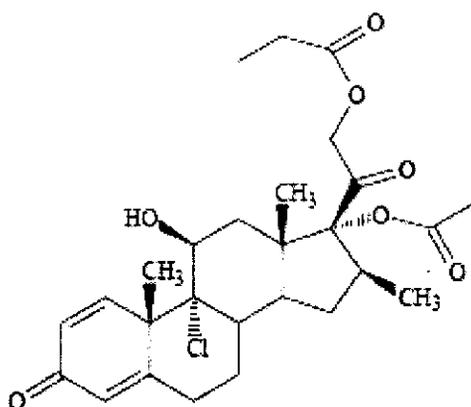
Characteristic		Model 4195
Lead Body Diameter		5 Fr (1.7 mm)
Lead Body Length		20-110 cm
Delivery System Recommended Inner Diameter		7 Fr I.D.
Fixation Method		Deployable lobes
Connector		IS-Unipolar
Steroid		30 µg beclomethasone dipropionate
Electrode	Material	Platinum Alloy
	Geometry	Tapered annular, platinized
	Surface Area	5.8 mm <sup>2</sup>
	Molded Tip Seal	Silicone Rubber

### **A. Device Component Description**

The Model 4195 is a 5 French, transvenous, unipolar, steroid-eluting, left ventricular, deployable lobe lead designed for pacing and sensing via the cardiac vein. The lead can be implanted using a guide wire or a stylet. The lead and accessories are supplied sterile. Each package contains one lead with stylet, anchoring sleeve, retention sleeve, two guide wire insertion tools, two acute retention clips (one is on the lead), one guide wire clip, one guide wire steering handle and extra stylets.

### **B. Drug Component Description**

The active drug component in the Model 4195 is beclomethasone 17,21-dipropionate (BDP). The chemical name of beclomethasone dipropionate is 9-chloro-11 $\beta$ ,17, 21-trihydroxy-16 $\beta$ -methylpregna-1,4-diene-3, 20 dione 17,21-dipropionate. The structural formula for beclomethasone 17,21-dipropionate is shown in Figure 1.



**Figure 1. Structure of Beclomethasone Dipropionate Anhydrous**

Beclomethasone 17,21-dipropionate is a diester of beclomethasone, a synthetic halogenated corticosteroid. Beclomethasone 17,21-dipropionate is a white to creamy white, odorless powder with a molecular formula of  $C_{28}H_{37}ClO_7$  and a molecular weight of 521.1. It is practically insoluble in water, freely soluble in chloroform; soluble in acetone and in dehydrated alcohol; sparingly soluble in alcohol.

The target dose of beclomethasone 17,21-dipropionate on each Model 4195 lead is 30  $\mu$ g (micrograms).

### **C. BDP Mechanism of Action**

Upon exposure to body fluids, the Beclomethasone dipropionate (steroid) elutes from the lead tip. Steroids suppress the inflammatory response that is believed to cause threshold rises typically associated with implanted pacing electrodes.

Beclomethasone dipropionate is a synthetic steroid of the glucocorticoid family. Glucocorticoid steroids have potent anti-inflammatory actions via direct and indirect effects on major inflammatory cells. While the mechanism of action of glucocorticoids is not fully understood, it is known that glucocorticosteroids bind to a cytoplasmic glucocorticoid receptor as well as to a membrane-bound receptor. Binding to the cytoplasmic receptor leads to receptor activation and translocation to the nucleus. The receptor interacts with specific DNA sequences (glucocorticoid responsive elements) within the regulatory regions of affected genes. Thus, glucocorticoids inhibit the production by multiple cells of factors that are critical in generating the inflammatory response.

## **VI. ALTERNATIVE PRACTICES AND PROCEDURES**

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An alternative for patients requiring implantation of a biventricular pacing system is the use of a commercially available left ventricular lead.

**VII. MARKETING HISTORY**

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The Medtronic Attain StarFix Model 4195 lead has not been marketed within the United States.

The Model 4195 lead is currently marketed outside the United States in the European Union, Canada and Australia. The lead has not been withdrawn from the market in any country for any reason related to the safety and effectiveness of the device.

**VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

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The potential clinical adverse events (listed in alphabetical order) resulting from use of transvenous leads include, but are not limited to, the following:

- Air embolism
- Avulsion of the endocardium, valve, or vein
- Cardiac dissection or perforation
- Cardiac tamponade
- Coronary sinus dissection
- Death
- Endocarditis or pericarditis
- Erosion through the skin
- Extra-cardiac muscle or nerve stimulation
- Fibrillation or other arrhythmias
- Heart block
- Heart wall or vein wall rupture
- Hematoma/seroma
- Infection
- Myocardial irritability
- Myopotential sensing
- Pericardial effusion or rub
- Pneumothorax
- Rejection phenomena (local tissue reaction, fibrotic tissue formation, pulse generator migration)
- Threshold elevation
- Thrombosis
- Thrombotic embolism
- Valve damage (particularly in fragile hearts)

Potential adverse events related to the lead and the programmed parameters include, but are not limited to, the following:

Potential adverse event	Indicator of potential adverse event
• Lead dislodgement	Intermittent or continuous loss of capture or sensing
• Lead dislodgement	Intermittent or continuous oversensing
• Lead conductor fracture or insulation failure	Intermittent or continuous loss of capture or sensing
• Threshold elevation or Exit block	Loss of capture

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Potential adverse events related to implant techniques that may damage the lead include, but are not limited to, the following:

<b>Implant techniques that may damage the lead</b>	<b>Possible effects on the lead</b>	<b>Corrective action to be considered</b>
Forcing the lead through the introducer/ delivery system	Electrode, conductor coil, indicator rings, lobe(s), push tubing, or insulation damage	Replace the lead
Use of too medial of an approach with venous introducer resulting in clavicle and first rib binding	Conductor coil fracture; insulation damage	Replace the lead
Puncturing the periosteum or tendon when using subclavian introducer approach	Conductor coil fracture; insulation or push tubing damage	Replace the lead
Stretching the retention sleeve or push tubing with the acute retention clip	Retention sleeve or push tubing damage	Replace the lead
Advancing the lead through the veins without the stylet or guide wire properly inserted	Tip distortion; insulation perforation; or damage to push tubing, lobes, or indicator rings	Replace the lead
Forcing advancement of the push tubing	Buckling of push tubing; difficulty in lobe deployment	Replace or deploy distal to the buckled section
Inserting the proximal end of the guide wire through the lead tip seal without using the guide wire insertion tool	Lead tip seal damage	Replace the lead
Advancing a stylet tip beyond the distal end of the lead tip seal	Lead tip seal damage	Replace the lead

In addition, renal failure due to contrast exposure is a potential risk associated with performing a venogram.

For the specific adverse events that occurred in the clinical studies, see Section X below.

## IX. SUMMARY OF PRECLINICAL STUDIES

A series of non-clinical laboratory and preclinical animal studies were performed on the Model 4195 lead and on the drug substance.

### A. Biocompatibility Studies

The materials used in the Model 4195 lead that are directly exposed to body tissues or fluids are summarized in Table 2. Most of the materials are identical to materials used on legally marketed Medtronic lead designs. Biocompatibility assessment was previously performed in accordance with ISO 10993-1, Biological Evaluation of Medical Devices: Evaluation and Testing. All materials were found to be biocompatible.

Biocompatibility testing has been performed for the new materials used in the 4195 lead. The testing performed was in accordance with ISO-10993, "Biological Evaluation of Medical Devices Part-1: Evaluation and Testing." All materials tested for use in the Model 4195 have passed biocompatibility testing.

**Table 2. Biocompatibility Information**

Component Name	Raw materials	Equivalent to currently marketed device	PMA # and approval date
Tip Electrode, Indicator Rings	Platinum / Iridium	4193 2187/2188 4092/4592 5024/5524 4024/4524 4074/4574 5076	P010015/S3, 05/02/02 P010015, 08/28/01 P830061/S27, 08/12/98 P850089/S9, 12/19/89 P830061/S12, 08/19/91 P830061/34, 07/23/02 P930039/S9, 08/31/00
Indicator Rings	Platinum / Iridium	4076 (Helix) 4194 (Electrode Coil)	P930039/S17, 02/09/04 P010015/S12, 08/20/04
Outer Insulation	Polyurethane	2187/2188 4092/4592 4024/4524	P010015, 08/28/01 P830061/S27, 08/12/98 P830061/S12, 08/19/91
Anchoring Sleeve and Retention Sleeve	Silicone Rubber with Barium Sulfate	6940 6942 6943/6945 6944 6947	P980016, 10/09/98 P920015/S12, 07/18/97 P920015/S13, 09/10/97 P920015/S17, 12/15/00 P920015/S24, 11/02/01
Connector Sleeve	Silicone Rubber	4193 2187/2188 4023/4523 4024/4524	P010015/S3, 05/02/02 P010015, 08/28/01 P830061/10, 08/07/91 P830061/S12, 08/19/91
Tip Seal	Silicone Rubber	4193 5076	P010015/S3, 05/02/02 P930039/S9, 08/31/00

Component Name	Raw materials	Equivalent to currently marketed device	PMA # and approval date
Connector Strain Relief	Silicone Rubber	4193 5076	P010015/S3, 05/02/02 P930039/S9, 08/31/00
Distal Tip of the Lead	Beclomethasone Dipropionate	Drug Master File, Master File Authorization Letter	N/A
		3830	P010036

### **B. In Vivo Pharmacokinetics**

Pharmacokinetics – The pharmacokinetics (local drug levels and systemic levels) of beclomethasone dipropionate and its metabolites following placement of the Model 4195 leads were not evaluated in human clinical trials.

### **C. Drug Interactions**

Drug interactions of beclomethasone 17,21-dipropionate with the Model 4195 lead have not been studied.

### **D. Lead Engineering Testing**

Environmental Conditioning: Model 4195 leads were subjected to four cycles of ethylene (EtO) sterilization and five cycles of thermal shock (-45°C to +70°C) prior to undergoing mechanical, electrical, and drug content testing. No damage or degradation to the test leads was noted following sterilization and thermal shock. Leads were then tested according to the summary below (Table 3). Tests were also conducted on the drug component part of the lead.

**Table 3. Bench Testing Summary for Attain StarFix Model 4195 Lead**

TEST	REQUIREMENT	RESULTS	SAMPLES TESTED
ETO Sterilization	No signs of damage or degradation upon visual examination (minimum magnification 3X) and must pass all subsequent mechanical and electrical tests	Passed	29 leads 127 subassemblies
Thermal Shock	No signs of damage or degradation upon visual examination (minimum magnification 3X) and must pass all subsequent mechanical and electrical tests	Passed	29 leads 149 subassemblies
Connector Mating Insertion/ Withdrawal	Insertion Forces $\leq$ 3.0 lbs Withdrawal Forces $\leq$ 2.5 lbs Sealing rings must not buckle or roll back during insertion	Passed	29 leads
Distal Seal Leak Test	No fluid should be observed on the coil or inside the inner lumen upon visual examination when tested in water. (minimum magnification of 3X).	Passed	29 leads

TEST	REQUIREMENT	RESULTS	SAMPLES TESTED
Retention Sleeve Leak Test	No fluid should be observed proximal of the retention sleeve with all three (3) sutures tied when tested in water. (minimum magnification of 3x).	Passed	33 subassemblies
Lobe Deployment Test	After the lead is hydrated, the lobes must fully deploy and undeploy 12 cycles with the lead positioned in a tortuous path model. There must be no damage to the lead noted upon visual examination (10x magnification minimum)	Passed	32 leads
Acute Retention Clip Engagement and Disengagement Test	When the acute clip is disengaged on the retention sleeve and the lead has been hydrated, the lobes must fully deploy and undeploy. There must be no damage to the lead, retention sleeve, or lobe deployment after engaging and disengaging the acute clip. (10x magnification minimum)	Passed	29 leads
Lead Composite Pull Test*	The lead must meet a minimum 1.0 lb tensile strength	Passed	29 leads
Push Tubing to Lead Body Pull Test*	The adhesive bond between the push tubing and lead body must meet a minimum 1.0 lb tensile strength	Passed	33 subassemblies
Push Tubing to Retention Sleeve Pull Test*	The adhesive bond between the push tubing and retention sleeve must meet a minimum 1.0 lb tensile strength	Passed	29 subassemblies
Conductor Joint Testing	Inner Coil/Electrode Tip, $\geq 3.0$ lb Inner Coil/Connector Pin, $\geq 2.5$ lb	Passed Passed	31 subassemblies By similarity to Model 4193
Anchoring Sleeve Suture Test*	$\geq 0.25$ lb minimum breakaway force Anchoring sleeve mobile on lead prior to suturing without sliding when the lead is held in a vertical position. There must be no damage to the coil or insulation noted upon visual examination (unaided eye)	Passed	29 leads
Retention Sleeve Suture Test*	$\geq 0.25$ lb minimum breakaway force There must be no damage to the coil or insulation noted upon visual examination (unaided eye)	Passed	33 subassemblies
Acute Retention Clip Holding Test	$\geq 0.25$ lb minimum breakaway force There must be no damage to the coil or insulation noted upon visual examination (unaided eye)	Passed	31 subassemblies
Lead Body Flex Test (Endocardial)	B50 flex life $\geq 2.0 \times 10^5$ cycles at a bend radius of 0.236"	Passed	22 leads

TEST	REQUIREMENT	RESULTS	SAMPLES TESTED
Connector Flex Test	> 82,000 cycles at 45° bend radius without coil fracture or intermittency	Passed	By similarity to Model 4193
Stylet Insertion / Withdrawal	<u>Straight Stylet</u> ≤ 100 grams in connector ≤ 300 grams in lead body.	Passed Passed	29 leads
Guide Wire Insertion/ Withdrawal	<u>Straight Guide Wire</u> ≤ 100 grams in connector ≤ 300 grams in distal tip. <u>Canted Guide Wire</u> ≤ 100 grams in connector ≤ 350 grams in distal tip.	Passed Passed Passed Passed	29 leads 29 leads
Composite Torsional Strength*	All lead samples must withstand at least 0.15 in.-oz. of torque, applied with clockwise and counter clockwise rotation, without sustaining any visible damage to any joint or component (when viewed with the unaided eye).	Passed	29 leads
Push Tubing to Lead Body Torsional Strength*	The push tubing to lead body bond must withstand at least 0.15 in.-oz of torque, applied with clockwise and counter clockwise rotation, without sustaining any visible damage to any joint or component (when viewed with the unaided eye).	Passed	33 subassemblies
DC Resistance	Unipolar 52 ± 9.0 ohms (78 cm)	Passed	29 leads
IS-1 Connector Leakage/ Medtronic AC Impedance Test Of Unipolar Leads	Impedance > 50 k Ohms	Passed	29 leads
Lead Tracking with Guide Wire and Medtronic Delivery System Compatibility	After hydration, all leads must successfully track over the guide wire and insert into the posterior lateral vein without any anomaly. All leads must be free of damage by visual inspection following use with the Medtronic Delivery System.	Passed	29 leads
Sterilization	The samples were exposed to one cycle of 100% EtO gas during the sterilization process. It was considered an overkill sterilization cycle and was performed in accordance with accepted standards. Devices must have a sterility assurance of at least 10 <sup>-6</sup> . Sterilization validation was performed by comparison to “worst case” devices.	Passed	20 partial leads (Model 4068). Proximal and distal ends of leads were cut and capped to create a worst case condition.

\*Testing performed after a 10 day soak

**E. Animal Testing**

The safety and biocompatibility of the Model 4195 lead was evaluated in a series of animal studies (Table 4). The results of biocompatibility, biostability, environmental stress cracking (ESC), electrical performance, gross and histopathological characteristics, and testing support the safety and biocompatibility of the Model 4195 lead. Additionally, steroid elution evaluation testing was also performed in animals to determine the amount of steroid remaining on the lead at various time points. The 4195 lead push tubing have demonstrated acceptable biostability as compared to controls. The Model 4195 lead demonstrated acceptable electrical performance (pace/sense thresholds), based on comparison to Model 4193 (P010015/S003) and Model 2187 (P010015) leads. The gross and histologic tissue changes observed were not excessive and were within the range expected for this procedure. The non-clinical animal testing of the Model 4195 demonstrates that the Model 4195 meets specification and performs appropriately. The results of these tests support the safety and biocompatibility of the Model 4195 lead.

**Table 4. Summary of Animal Studies**

Study Number / Name	Type/Number of Animals	Number of Leads	Follow-up Duration / Procedure	Acceptance Criteria	Results
0081D0027	Canine Test / Control: 16	Test: 51 (Model 4195) Control: 13 (Model 4023)	All canines terminated after implant durations of at least 26 weeks.	The canines were sacrificed after study durations of 26 to 33 weeks and gross and histopathological assessments were made.	The gross and histologic tissue changes observed were not excessive and were within the range expected for this procedure.
4195 Canine Biostability Final Report	Canine Test / Control: 16	Test: 51 (Model 4195) Control: 13 (Model 4023)	All canines terminated after implant durations of at least 26 weeks.	After 6 month implant in canines, the material demonstrate no evidence of Environmental Stress Cracking, Metal-Ion Oxidation or other phenomena that can be construed as unacceptable degradation.	4195 lead push tubing have demonstrated acceptable biostability as compared to controls.
Accelerated 12 and 26-week ESC Study Final Report	Rabbit Test / Control: 7	Test: 2 lots tubing Control: 1 lot tubing	Explant test samples at 12 weeks and the remaining at 26 weeks.	Demonstrate acceptable biostability if the test material performs equivalent or better than the test material. ESC level determined using optical microscopy.	4195 lead push tubing have demonstrated acceptable biostability as compared to controls.

Study Number / Name	Type/Number of Animals	Number of Leads	Follow-up Duration / Procedure	Acceptance Criteria	Results
0120A0265	Canine Test / Control: 6	Test: 6 Control: N/A	Gathered electrical data at 0, 1, 2, 3, 4, 8, 12 weeks post implant 15, 16 and 25 week histology	Acceptable electrical performance (pacing threshold) as compared to other left ventricular lead Model 4193 (steroid eluting cardiac vein lead) and lead Model 2187 (steroid free cardiac vein lead).	The Model 4195 lead demonstrated acceptable electrical performance based on comparison to Models 4193 and 2187 leads. The gross and histologic tissue changes observed were not excessive and were within the range expected for this procedure.
S1189 Model 4195 In-Vivo Steroid Evaluation	Canine Test / Control: 12	Test: 12 Control: N/A	Removed 4 leads at each time point, 5 hours, 7 days and 4 weeks.	N/A	The gross examination indicated tissue changes were not excessive and consistent with a left heart lead implant procedure.
Lead Model 4195 Canine Study in-vivo Elution Results	Canine Uses leads from previous animal study	Test: Uses 12 leads from previous animal study  Control: 4 lead from same BDP batch (leads not implanted)	Uses leads from previous animal study	N/A	An elution curve was developed. Less than 2.08 micrograms of BDP remaining after 4 weeks.
Acute Pass / Pull Beclomethasone Steroid Assay Study	Sheep Test/Control: 1	Test: 5 Control: 5 (leads not implanted)	Insert lead in great cardiac vein, then remove, repeat for a total of 6 pass/pulls.	N/A	13.7 +/-4.3 micrograms BDP remaining.

The preclinical laboratory testing of the Model 4195 demonstrates that the Model 4195 meets specification and performs appropriately.

### **E. Finished Product Drug Testing**

The results of the Active Pharmaceutical Ingredient (API) testing and finished product drug testing of the Model 4195 lead are presented in Table 5.

**Table 5. Chemistry Manufacturing and Controls Testing For Model 4195**

TEST	REQUIREMENT	RESULTS	SAMPLES TESTED
Drug Substance Identity	Reversed-phase high performance liquid chromatography (HPLC) testing was conducted to verify the identity of beclomethasone dipropionate.	Passed	3 lots of drug substance
Finished Product Elution	An assay was developed to measure the in vitro release kinetics of beclomethasone dipropionate from the Model 4195 lead. Analysis was conducted to ensure that internal specifications were met.	Passed	9 lots of finished product
Finished Product Content/Related Substances	Testing was performed to identify and quantify the drug related substances on the Model 4195 lead and to ensure that the product met internal specifications for finished product release.	Passed	9 lots of finished product
Finished Product Content Uniformity	Testing was conducted to verify process used reproducibly deposited drug material within a drug application lot. The lots were examined to ensure that they met the internal specification for drug content at the time of testing.	Passed	9 lots of finished product
Finished Product Residual Solvents	The amount of solvent used in the manufacture of the Model 4195 was evaluated to ensure that it was below the residual amount allowed by ICH (International Conference of Harmonization) guidance Q3C: Impurities: Guideline for Residual Solvents	Passed	9 lots of finished product

## **X. SUMMARY OF PRIMARY CLINICAL STUDY**

### **A. Study Design**

The Model 4195 lead study was a prospective, multi-center (20 US, 4 Canada, 1 Italy) clinical trial using objective performance criteria (OPC) to evaluate the safety and efficacy of the Model 4195 left ventricular (LV) lead. Data from a previous LV lead study for Model 2187 and 2188 leads (P010015) were used to establish the Model 4195 lead objective performance criteria (OPC) which is reflected in the primary safety and efficacy endpoints. Therefore, control subjects were not used in this study. Candidates for implant included subjects of both genders with heart failure who were classified as New York Heart Association (NYHA) functional class III and IV, and who met all inclusion and no exclusion criteria. All subjects with a successful Model 4195 lead implant were evaluated at pre-hospital discharge, 1 month, 3 months, 6 months, and every 6 months thereafter, until study completion.

## **B. Subject Selection**

Subjects of both genders who were indicated for CRT and who met all inclusion and no exclusion criteria were eligible for a Model 4195 lead implant attempt.

## **C. Inclusion Criteria**

- Demonstrated intrinsic QRS duration  $\geq 130$  ms (test documented within 6 months of Baseline)
  - Left Ventricular Ejection Fraction (EF)  $\leq 35\%$  (test documented within 12 months of Baseline)
  - Subject is diagnosed with NYHA Class III or IV despite optimal medical therapy which is defined as:
    - ACE inhibitor or Angiotensin Receptor Blocker (ARB), if tolerated, for at least one month prior to implant
    - Beta-blockers for at least three months preceding implant, if tolerated, and stable for one month. Stable is defined as no upward titration of beta-blockers
- OR
- Subject has an urgent medical need for an ICD that precludes waiting the one or three months for medication requirement for ACE inhibitor, ARB or beta-blocker
  - Subject is indicated for ICD implantation for the treatment of life threatening ventricular arrhythmias<sup>1</sup> (required only if subject will receive an ICD)
  - Subject has signed and dated the study Informed Consent
  - Subject is 18 years of age or older
  - Subject is expected to remain available for follow-up visits
  - Subject is willing and able to comply with the protocol

## **D. Exclusion Criteria**

- Subjects with a previous complete atrial based biventricular CRT system
- Subjects with a previous LV lead implanted or previous implant attempt within 30 days of implant or ongoing adverse events from previous unsuccessful attempt
- Subjects with unstable angina pectoris or who have had an acute MI within the past month
- Subjects that have had a CABG or PTCA within the past three months
- Subjects with chronic (permanent) atrial arrhythmias

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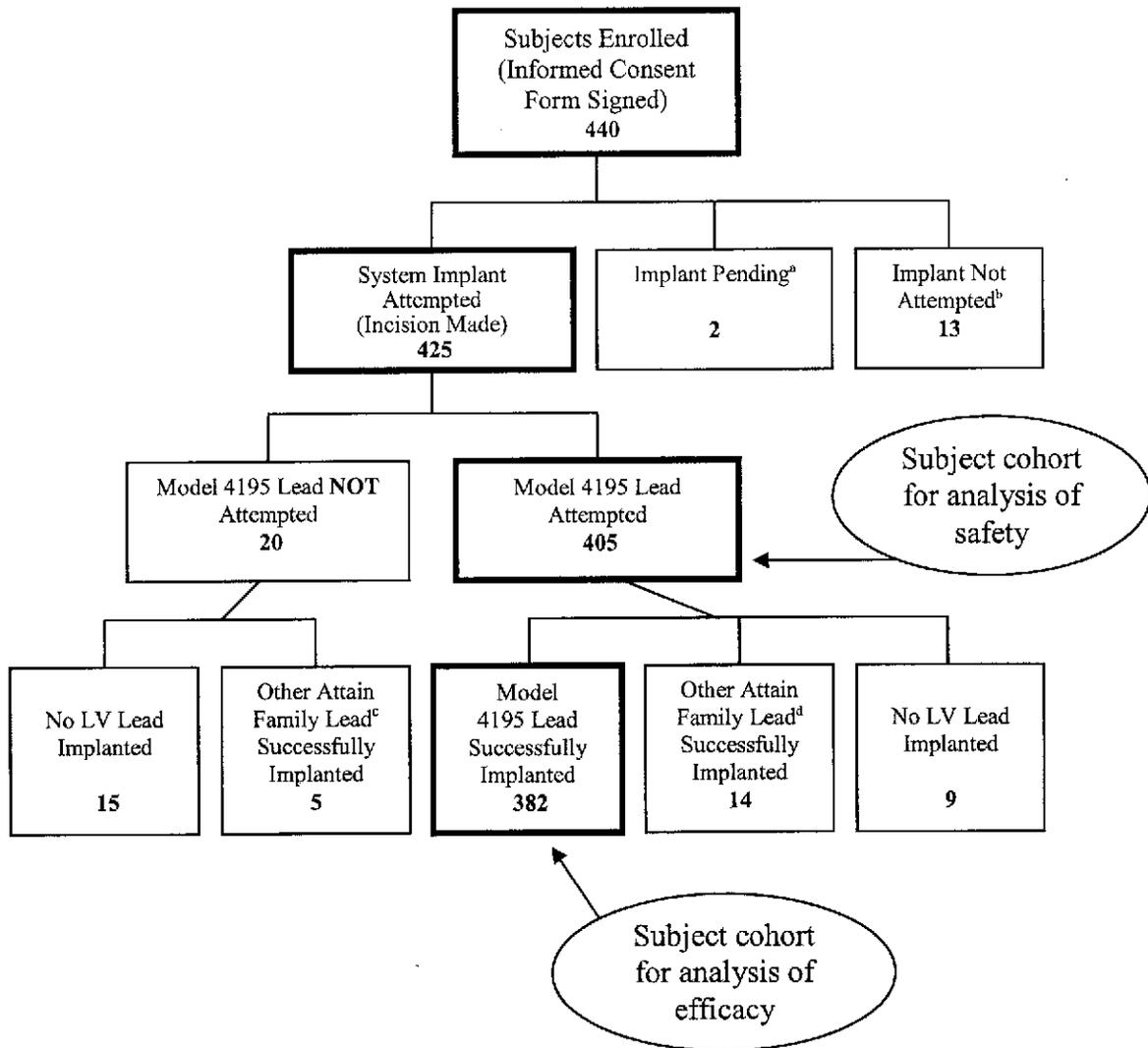
<sup>1</sup> In accordance with Class I or II ICD indications as specified in the current American College of Cardiology / American Heart Association / Heart Rhythm Society (ACC/AHA/HRS) practice guidelines at the time of implant.

- Subjects with contraindications for standard transvenous cardiac pacing (e.g. mechanical right heart valves)
- Subjects contraindicated for < 100 micrograms beclomethasone dipropionate
- Post heart transplant subjects (subjects waiting for heart transplant are allowed in the study)
- Subjects enrolled in any concurrent drug and/or device study that may confound the results of this study
- Subjects with a terminal illness who are not expected to survive more than six months
- Women who are pregnant, or have a positive pregnancy test within 7 days prior to implant, or with child bearing potential and who are not on a reliable form of birth control (All women of child bearing potential must undergo a pregnancy test within 7 days prior to implant.)
- Subjects unable to tolerate an urgent thoracotomy

**E. Subject Enrollment and Follow-up**

Data was collected for a total of 440 subjects enrolled with 425 subjects having implant attempts. A total of 405 subjects underwent a lead implant attempt with the Model 4195 lead. A summary of enrollment status is presented in Figure 2. After providing consent and a successful baseline evaluation, eligible subjects underwent a cardiac resynchronization therapy (CRT) system implant attempt. Physicians were advised that any market-released right atrial lead, any market-released Medtronic right ventricular lead, and any market-released Medtronic CRT/CRT-D device could be implanted. The Model 4195 lead could also be attempted but was not required. If the Model 4195 lead was not attempted at the time of implant or was unable to be implanted, any market-released LV lead labeled for biventricular pacing systems could have been used. These patients were not included in the safety and effectiveness analyses for the Model 4195 lead. The physicians were trained to make their LV lead selections based on experience, handling preference and subject anatomy.

**Figure 2. Enrollment Status**  
(As of March 5, 2007)



<sup>a</sup> Two subjects were enrolled but pending implant at the time of data cut-off.

<sup>b</sup> Eleven subjects did not meet inclusion/exclusion criteria after consent and two subjects did not continue with an implant attempt (one subject had an increased BUN/creatinine level at the time of scheduled implant and the investigator chose not to proceed with an investigational implant, one subject's procedure was aborted after a venogram showed occlusion of the left subclavian vein).

<sup>c</sup> The "Other Medtronic Attain Family Leads" implanted in the subjects who were not attempted with the Model 4195 lead included three Model 4194 leads and two Model 4193 leads.

<sup>d</sup> The "Other Medtronic Attain Family Leads" implanted in the subjects attempted with the Model 4195 lead included 11 Model 4193 leads, two Model 4194 leads, and one Model 2187 lead.

**F. Objectives**

As pre-specified in the Clinical Investigational Plan, the following were the primary and secondary objectives for the Model 4195 lead study.

## **G. Primary Objectives**

### **Safety**

The Model 4195 Lead will be considered safe if the complication-free survival from lead-related complications at three months is greater than or equal to 80%.

### **Effectiveness**

The Model 4195 Lead will be considered effective if the mean left ventricular voltage threshold (at 0.5 ms) at the three-month visit is less than or equal to 2.5 volts (not including loss of capture values).

## **H. Secondary Objectives**

The secondary objectives were descriptive in nature and were intended to provide additional information about the Model 4195 lead. There were no established performance requirements related to the secondary objectives.

- To evaluate the implant success rate of the Model 4195 Lead
- To evaluate the total implant, fluoroscopy, cannulation, and LV placement time for the Model 4195 Lead
- To evaluate handling characteristics and lobe deployment of the Model 4195 Lead
- To evaluate all adverse events (AEs) occurring during the clinical study (excluding unavoidable adverse events)
- To evaluate the electrical performance (sensing, LV pacing impedance, LV pulse width threshold, and phrenic nerve/diaphragmatic stimulation) of the Model 4195 Lead

## **I. Data Analysis and Results**

The clinical study for the Medtronic Attain StarFix Model 4195 lead was conditionally approved for 50 subjects at 10 centers on May 27, 2004 under G040036. The study approval was expanded to 20 centers and 250 US subjects on January 6, 2005. Medtronic also collected OUS data for up to 50 subjects at 5 centers in Canada and Europe. Per the Clinical Investigational Plan, the primary safety and effectiveness objectives were evaluated when the study's critical sample size was met. This analysis had a cut-off date of July 6, 2005 and all primary safety and efficacy objectives were met. Medtronic received approval for a Continued Access Phase (CAP) for the existing 20 US centers to enroll up to 175 additional subjects (425 total US subjects) on January 5, 2006. The original PMA was submitted on December 26, 2006 and included data for 296 IDE and CAP enrolled subjects as of a cut-off date of August 29, 2006. In the course of reviewing the PMA, additional safety data and confirmatory efficacy data were submitted for the 440 enrolled subjects (IDE & CAP cohorts) as of a cut-off date of March 5, 2007. The performance and efficacy of the Model 4195 lead was consistent between the July 6, 2005, August 29, 2006 and

March 5, 2007 cut-off dates. The data presented in this summary are based on the 440 enrolled subjects as of a cut-off date of March 5, 2007 since this represents the most complete data set reviewed by FDA for approval of the Model 4195 lead.

**Demographic Data**

All subjects who underwent an implant attempt (425) were included in the study population analyses. The demographics for this cohort are presented in Table 6. Subjects ranged in age from 35.7 to 89.7 years, with a mean age of 68.6 years. 296 of the subjects (69.6%) were male and 129 of the subjects (30.4%) were female. The majority of subjects were NYHA Class III (408, 96.0%), and the remaining subjects were NYHA Class IV (17, 4.0%). The subject cohort had a mean intrinsic QRS width of 155.8 ms (SD = 19.6) and a mean LV ejection fraction of 23.3% (SD = 6.4).

**Table 6. Subject Demographics**  
(As of March 5, 2007, N = 425)

Category		Subjects with an Implant Attempt
Gender, N (%)	Male	296 (69.6%)
	Female	129 (30.4%)
Age, years	Mean	68.6
	Standard deviation	11.4
	Range	35.7 – 89.7
NYHA functional classification, N (%)	Class III	408 (96.0%)
	Class IV	17 (4.0%)

**Primary Safety and Effectiveness Objective Results**

A summary of primary safety objective and effectiveness objective results are presented in Table 7.

**Table 7. Summary of Primary Objectives Results at Three Months**  
(As of March 5, 2007)

Primary Objective	Results
<b>Safety:</b> The Model 4195 Lead will be considered safe if the complication-free survival rate from lead related complications at three months is greater than or equal to 80%	Percent of Subjects Free of Complications = <b>96.8% (N=405)</b> 95% LCB = <b>94.4%</b> 13 lead related events in 12 subjects
<b>Effectiveness:</b> The Model 4195 Lead will be considered effective if the mean left ventricular (LV) voltage threshold (at 0.5 ms) at the three month visit is less than or equal to 2.5 volts (not including loss of capture values)	Mean LV voltage threshold = <b>1.3 V (N=304)</b> 95% UCB = <b>1.4 V</b>

**Safety:** The safety of the Model 4195 lead was evaluated by investigator documentation of all Model 4195 lead related adverse events (see Section J). All subjects with a Model 4195 lead attempt were included in this evaluation. Table 11 presents the Kaplan-Meier estimate of freedom from lead related complications through 30 months. At 3 months, the primary objective end point, 12 subjects had experienced a total of 13 Model 4195 lead related complications (Tables 12 and 13).

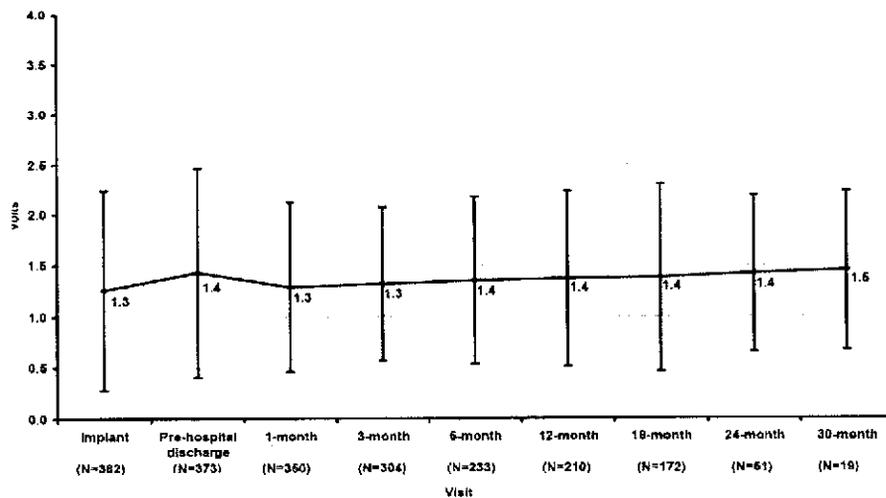
**Effectiveness:** Table 8 and Figure 3 summarize the voltage thresholds, measured at implant and at all protocol required follow-up visits. Only subjects with pacing thresholds captured at 0.5 ms were included in the analysis. Subjects with unable-to-capture (UTC) thresholds were not included in the efficacy analysis for the corresponding visit.

**Table 8. Voltage Threshold at 0.5 ms**  
(As of March 5, 2007)

Visit	N	Mean (volts)	Median	Std. Dev.	Range	95% UCB
Implant	382	1.3	0.9	1.0	0.2 – 6.9	1.4
Pre-hospital discharge	373	1.4	1.0	1.0	0.5 – 6.0	1.5
1 month	350	1.3	1.0	0.8	0.5 – 6.0	1.4
<b>3 month*</b>	<b>304</b>	<b>1.3</b>	<b>1.0</b>	<b>0.8</b>	<b>0.5 – 6.0</b>	<b>1.4</b>
6 month	233	1.4	1.0	0.8	0.5 – 6.0	1.5
12 month	210	1.4	1.0	0.9	0.5 – 6.0	1.5
18 month	172	1.4	1.0	0.9	0.5 – 6.0	1.5
24 month	61	1.4	1.0	0.8	0.5 – 5.0	1.6
30 month	19	1.5	1.0	0.8	0.5 – 3.0	1.8

\* Exceeds acceptance criteria of 2.5 V.

**Figure 3. Model 4195 lead pacing threshold data at 0.5 ms.**  
(As of March 5, 2007, Mean +/- one standard deviation)



## Secondary Objective Results

Table 9 presents a summary of the secondary objectives results. The secondary objectives summarize the Attain family and Model 4195 lead implant success, lead placement and procedure time, lead handling and lobe deployment, additional electrical performance, and all adverse events reported in the study.

The results of the secondary objectives confirmed that the Model 4195 lead can be successfully and safely implanted, and that electrical performance values were comparable to those of Medtronic market-approved LV leads. Specifically, the LV pacing thresholds (Mean  $\pm$  SD) for the Model 4193 and Model 4194 leads at 3 months were 1.4 V  $\pm$  1.1 and 1.6 V  $\pm$  1.1, respectively; whereas the LV mean pacing threshold at 3 months for the Model 4195 lead was 1.3 V  $\pm$  0.8.

**Table 9. Summary of Secondary Objectives Results at Three Months**  
(As of March 5, 2007)

Secondary Objective	Results
Evaluate the Attain leads implant success	All transvenous LV leads success = 94.4% (401/425) All transvenous LV leads success after cannulation = 95.9% (401/418) Attain family success = 94.4% (401/425) Model 4195 lead success = 94.3% (382/405)
Evaluate total implant, fluoroscopy, cannulation and Model 4195 lead placement time (mean $\pm$ standard deviation)	Cannulation time = 8.1 min $\pm$ 14.6 (N=382) Fluoroscopy time = 22.5 min $\pm$ 17.2 (N=377) Model 4195 lead placement time = 12.6 min $\pm$ 12.9 (N=382) Total implant time = 115.9 min $\pm$ 48.0 (N=382)
Evaluate lead handling and lobe deployment	Ability to Push (Good or Fair) = 97.4% (381/391) Ability to Navigate (Good or Fair) = 96.9% (379/391) Stability (Good or Fair) = 99.2% (383/386) Ability to Deploy/Undeploy (Good or Fair) = 96.6% (374/387) Acceptability = 98.3% (397/404) Number of deployments per unique lead = 1.9 $\pm$ 1.7
Evaluate the electrical performance of the Model 4195 LV lead (mean $\pm$ standard deviation)	<b>Model 4195 Lead Extra-cardiac Stimulation Threshold at Implant</b> 33/382 (8.6%) experienced extra-cardiac stimulation at implant Mean stimulation threshold for the 33 subjects = 6.0 V $\pm$ 2.1
Voltage thresholds measured at 0.5 ms Pulse width thresholds measured at 3.0 V	<b>Model 4195 Lead Electrical Performance at Implant</b> R-Wave Amplitude = 16.4 mV $\pm$ 5.4 (N = 365) Impedance = 772.2 Ohms $\pm$ 262.3 (N = 381) Voltage Threshold = 1.3 V $\pm$ 1.0 (N = 382)
	<b>Model 4195 Lead Electrical Performance at Discharge</b>

Secondary Objective	Results
	R-Wave Amplitude = 14.5 mV ± 5.1 (N = 365) Impedance = 559.3 Ohms ± 187.1 (N = 378) Voltage Threshold = 1.4 V ± 1.0 (N = 373) Pulse Width Threshold = 0.16 ms ± 0.23 (N = 366)
	<b>Model 4195 Lead Electrical Performance at 1 month</b>
	R-Wave Amplitude = 16.3 mV ± 5.6 (N = 341) Impedance = 482.7 Ohms ± 122.7 (N = 355) Voltage Threshold = 1.3 V ± 0.8 (N = 350) Pulse Width Threshold = 0.13 ms ± 0.14 (N = 348)
	<b>Model 4195 Lead Electrical Performance at 3 months</b>
Evaluate the electrical performance of the Model 4195 LV lead (mean ± standard deviation)  Voltage thresholds measured at 0.5 ms Pulse width thresholds measured at 3.0 V	<b>Model 4195 Lead Electrical Performance at 3 months</b>
	R-Wave Amplitude = 16.4 mV ± 5.6 (N = 292) Impedance = 503.3 Ohms ± 134.7 (N = 310) Voltage Threshold = 1.3 V ± 0.8 (N = 304) Pulse Width Threshold = 0.13 ms ± 0.11 (N = 305)
	<b>Model 4195 Lead Electrical Performance at 6 months</b>
	R-Wave Amplitude = 17.1 mV ± 6.3 (N = 222) Impedance = 515.7 Ohms ± 141.4 (N = 240) Voltage Threshold = 1.4 V ± 0.8 (N = 233) Pulse Width Threshold = 0.15 ms ± 0.15 (N = 234)
	<b>Model 4195 Lead Electrical Performance at 12 months</b>
	R-Wave Amplitude = 16.9 mV ± 6.0 (N = 199) Impedance = 526.3 Ohms ± 142.7 (N = 213) Voltage Threshold = 1.4 V ± 0.9 (N = 210) Pulse Width Threshold = 0.14 ms ± 0.14 (N = 206)
	<b>Model 4195 Lead Electrical Performance at 18 months</b>
	R-Wave Amplitude = 17.4 mV ± 6.0 (N = 161) Impedance = 536.6 Ohms ± 146.5 (N = 178) Voltage Threshold = 1.4 V ± 0.9 (N = 172) Pulse Width Threshold = 0.15 ms ± 0.19 (N = 171)
<b>Model 4195 Lead Electrical Performance at 24 months</b>	
R-Wave Amplitude = 19.2 mV ± 6.3 (N = 57) Impedance = 593.1 Ohms ± 292.8 (N = 62) Voltage Threshold = 1.4 V ± 0.8 (N = 61) Pulse Width Threshold = 0.18 ms ± 0.20 (N = 61)	
<b>Model 4195 Lead Electrical Performance at 30 months</b>	
R-Wave Amplitude = 20.1 mV ± 7.6 (N = 19) Impedance = 580.6 Ohms ± 203.2 (N = 19) Voltage Threshold = 1.5 V ± 0.8 (N = 19) Pulse Width Threshold = 0.16 ms ± 0.14 (N = 19)	

Secondary Objective	Results
Summarize all adverse events reported during the clinical study	<b>Complications (531 events in 202 subjects)</b>
	Model 4195 Lead Related = 16 events Model 4193 Lead Related = 1 event RV Lead Related = 9 events RA Lead Related = 7 events CR Device Related = 2 events System Related = 4 events Procedure Related = 32 events Implant Tool Related = 3 events Therapy Related = 4 events System Modification / Explant Procedure Related = 2 events Non-System Related = 451 events
	<b>Observations (686 events in 246 subjects)</b>
	Model 4195 Lead Related = 65 events RV Lead Related = 6 events RA Lead Related = 12 events CR Device Related = 7 events System Related = 5 events Procedure Related = 51 events Implant Tool Related = 4 events Non-System Related = 536 events

**J. Adverse Events Summary**

The following section includes a summary of adverse events that were reported in the clinical study of the Attain StarFix Model 4195 lead. The dataset included adverse events for all subjects between the first implant attempt, July 7, 2004, and the data cut-off date of March 5, 2007. During this period of time a total of 425 subjects underwent an pacing system implant attempt. Of these, 405 subjects had a Model 4195 lead implant attempt, and 382 subjects were successfully implanted with a Model 4195 lead. As of March 5, 2007, evaluation of the Model 4195 lead included 4759.9 device months of experience. Subject follow-ups ranged from 0 to 31.3 months and averaged  $11.8 \pm 9.4$  months (median = 12.5 months).

A total of 1217 adverse events were reported in the subject cohort and are presented in Table 2. Five hundred thirty-one (43.6%) of the events were classified as complications and 686 (56.4%) were classified as observations.

For the purpose of the Model 4195 lead study, an adverse event was defined as any undesirable clinical occurrence in a subject, whether or not related to the investigational device. Adverse events were coded by the center and then further classified by relatedness. Medtronic reviewed each event and the treatment associated with the event to determine if the event was a complication or an observation. The Adverse Event Advisory Committee adjudicated this classification for every adverse event. The definition for each follows:

**Complication:** An adverse event that results in invasive intervention, or the termination of significant device function regardless of other treatments. Intravenous (IV) and intramuscular (IM) therapies are considered invasive treatment.

**Observation:** An adverse event that is not a complication.

**Relatedness:** All adverse events were classified by their relatedness to the components, the CR system, implant tools, therapy, or procedure.

Table 10 provides a summary of all adverse events including incidence rates by complication and observation. Incidence rate is defined as the number of unique adverse events divided by subject months of exposure to the risk and normalized to 100 device months. The number of subjects at risk for each event can be found in the footnotes to Table 10.

**Table 10. Summary of All Adverse Events**  
(As of March 5, 2007)

Relatedness	Complications		Observations	
	Number of Events	Incidence Rate per 100 Device Months	Number of Events	Incidence Rate per 100 Device Months
Model 4195 LV lead <sup>1</sup>	16	0.34	65	1.37
Model 4193 LV lead <sup>2</sup>	1	7.00	0	0
Right ventricular lead <sup>3</sup>	9	0.19	6	0.13
Right atrial lead <sup>3</sup>	7	0.15	12	0.25
Cardiac resynchronization device <sup>4</sup>	2	0.04	7	0.15
Cardiac resynchronization system <sup>4</sup>	4	0.08	5	0.10
Implant procedure <sup>3</sup>	32	0.67	51	1.07
Implant tool <sup>3</sup>	3	0.06	4	0.08
System modification / explant procedure <sup>3</sup>	2	0.04	0	0
Therapy <sup>4</sup>	4	0.08	0	0
Not related to cardiac resynchronization system <sup>5</sup>	451	9.38	536	11.14
<b>Total</b>	<b>531</b>	<b>11.04</b>	<b>686</b>	<b>14.26</b>

<sup>1</sup> 405 subjects experienced a Model 4195 lead implant attempt and were at risk for this event.

<sup>2</sup> 30 subjects experienced a Model 4193 lead implant attempt and were at risk for this event.

<sup>3</sup> 425 subjects experienced an implant attempt and were at risk for this event.

<sup>4</sup> 401 subjects received a cardiac resynchronization device and were at risk for this event.

<sup>5</sup> 440 subjects were enrolled in the study and were at risk for this event.

The 405 subjects who underwent a Model 4195 lead attempt were included in the safety endpoint analysis. Table 11 presents the results of the safety endpoint analysis – freedom from lead related complications at three months. At three months, twelve (12) subjects had experienced a total of thirteen Model 4195 related complications.

**Table 11. Freedom from Model 4195 Lead Related Complications**  
(As of March 5, 2007)

Survival Interval	Cumulative Number of Subjects with Events	Percent of Subjects Free of Complications	95% Lower Confidence Bound (1-sided)
1 month	10	97.4%	95.2%
<b>3 months*</b>	<b>12</b>	<b>96.8%</b>	<b>94.4%</b>
6 months	12	96.8%	94.4%
12 months	12	96.8%	94.4%
18 months	14	95.5%	92.3%
24 months	14	95.5%	92.3%
30 months	15	91.9%	92.3%

\*Exceeds acceptance criteria of 80%.

Results from an additional analysis, which used the binomial method to summarize the percent of subjects free of Model 4195 lead related complications at three months are presented in Table 12.

**Table 12. Binomial Estimate of Model 4195 Lead Related Complication Free Probability**  
(As of March 5, 2007)

Subjects with Model 4195 Lead Attempt (N=405)	Number of Subjects	Number of Subjects with Model 4195 Lead Related Complications at 3 Months
Number of subjects with a Model 4195 lead implanted and complication-free data at 3-months	319	12 (Percent of Subjects Free of Complications = 96.2%)
Number of subjects with a Model 4195 lead implanted but were not yet followed to 3-months and did not have Model 4195 related complications	63	0
Number of subjects implanted with other LV leads	Model 2187	0
	Model 4193	0
	Model 4194	0
No LV lead implanted	9	0
<b>Total</b>	<b>405</b>	<b>12</b> <b>(Overall Percent of Subjects Free of Complications at 3 Months= 97.0%)</b>

Table 13 summarizes the Model 4195 lead related complications at three months and their treatments.

**Table 13. Treatment of Model 4195 Lead Related Complications through 3 Months**  
(As of March 5, 2007, N = 13)

Event	Treatment	N
Lead dislodgement	Lead Replaced	2
	Lead Repositioned	1
Failure to capture, loss of capture	Lead Replaced	1
	Lead Repositioned	1
Extra-cardiac stimulation	Lead Removed	1
	Lead Replaced	2
	Lead Repositioned	2
	Lead Capped	1
	Lead Temporarily Programmed Off	2

With regard to lead dislodgement, a total of three (3) Model 4195 lead dislodgements were reported during the Model 4195 lead study, which resulted in a dislodgement rate of 0.8%. The first two (2) dislodgements occurred within the first five (5) implants of the clinical study. As a result of these early events, recommendations for lead placement were established and communicated to investigators (see Attain StarFix Model 4195 Lead Technical Manual, Section 9.9). Only one (1) additional dislodgement occurred during the course of the study, and in this case one of the two placement recommendations was not followed.

**K. Device Failures and Replacements**

A total of 25 implanted Model 4195 leads were removed from 24 subjects and returned to Medtronic. Three explants were due to extra-cardiac stimulation, two (2) due to lead dislodgement, two (2) due to failure to capture/loss of capture, five (5) as a result of system infection, nine (9) as a result of subject death (2 leads were implanted in one subject), one (1) due to pocket erosion, one (1) due to lead fracture, and one (1) due to a heart transplant. Some of the returned leads appeared to have damage related to the explant procedure, and one (1) of the 17 leads that was returned to Medtronic for analysis showed a defect that would have resulted in a device failure, lead fracture. One (1) additional lead fracture was reported after the data cut-off and was analyzed as part of the review. A summary of clinical study lead modification and extraction experience for the Model 4195 lead is presented in the section below.

**L. Summary of Model 4195 Lead Modifications**

As with other LV leads, chronic repositioning or removal of leads may be difficult because of fibrotic tissue development. Of the 382 subjects successfully implanted with a Model 4195 lead, 19 subjects underwent 21 Model 4195 lead modification attempts.

Fifteen (15) of the 19 subjects (79%) had a Model 4195 lead successfully repositioned or removed. In the first 30 days following implant, 100% of the leads were successfully modified. A summary of the successful modification attempts from 0 to 910 days post-implant is outlined in Table 14.

**Table 14: Summary of Successful Modifications by Time Post Implant**  
(As of March 5, 2007, N=16)

Reason for Modification	Days Post Implant	Extraction Method Used	Outcome
Failure to capture, loss of capture	0	Traction	Successfully removed
Dislodgement	1	Traction	Successfully removed
Dislodgement	1	Traction	Successfully removed
Dislodgement	1	Traction	Successfully repositioned
Extra-cardiac stimulation	1	Traction	Successfully repositioned
Extra-cardiac stimulation	8	Traction	Successfully removed
Extra-cardiac stimulation	16	Traction	Successfully repositioned
Infection	21	Traction	Successfully removed
Infection	22	Traction	Successfully removed
Failure to capture, loss of capture	23	Traction	Successfully repositioned
Extra-cardiac stimulation	37	Traction	Successfully removed
Infection	50	Traction	Successfully removed
Extra-cardiac stimulation	66	Traction	Successfully removed
Infection	92	Traction	Successfully removed
Extra-cardiac stimulation	581	Traction	Successfully repositioned
Infection	910	Laser in SVC, RA; counter-traction in CS with sheath	Successfully removed

The Model 4195 lead was capped in five (5) cases after an unsuccessful modification attempt. The lead that was capped at 889 days post-implant was subsequently removed at 910 days using laser in the superior vena cava (SVC) and right atrium (RA), and counter-traction in the coronary sinus (CS). A summary of the five (5) unsuccessful modification attempts is outlined in Table 15.

**Table 15: Summary of Unsuccessful Modifications by Time Post Implant**  
(As of March 5, 2007, N=5)

Reason for Modification	Days Post Implant	Extraction Method Used	Outcome
RA lead reposition, non-response to CRT therapy	81	Traction	Capped, lead could not be removed by traction alone
Pocket erosion	478	Traction with locking stylet	Capped, with locking stylet, lead could not be removed by traction alone
Failure to capture, loss of capture	546	Traction	Distal segment of lead capped at clavicle
Lead fracture	795	Traction	Capped, lead could not be removed by traction alone
Sub-optimal LV lead placement	889	Traction	Capped, lead could not be removed by traction alone (later removed at 910 days)

Of the 21 modification attempts, no lead related complications were attributed to attempts at repositioning or removing the Model 4195 lead. One subject developed sepsis following an attempt to reposition the generator and Model 4195 lead (889 days post-implant). The same subject developed anemia following a second modification procedure (910 days post-implant) for complete removal of the CRT system.

Though there were not lead related complications attributed to repositioning or removing the Model 4195 lead, the novel fixation mechanism may introduce unique risks and difficulty associated with late revision and removal. Therefore, referral to an experienced extraction center is recommended. The risk and difficulty of removing the Medtronic Attain StarFix Model 4195 lead following long-term implant will be characterized in a post-approval study.

**M. Subject Exits and Deaths**

Of the 440 subjects enrolled, 101 subjects exited the study. Thirteen (13) subjects exited prior to any implant attempt, 20 exited because they did not have a Model 4195 lead attempted, and 22 exited because they did not have a successful Model 4195 lead implant. Eight (8) subjects had a Model 4195 lead explanted and were subsequently exited from the study. Two (2) subjects voluntarily withdrew from the study. Thirty-six (36) subjects exited due to death. Eighteen (18) of the deaths were classified as cardiac related, 15 deaths as non-cardiac related, and 3 deaths as having an unknown cause. None of the subject deaths were thought to be LV lead related. One subject death, caused by a cerebrovascular accident, was considered to be related to the CRT system implant procedure.

#### **N. Conclusion**

As of March 5, 2007, 440 subjects were enrolled into the Model 4195 lead study. Of these subjects, 405 had a Model 4195 lead attempt with 382 successfully implanted (94.3% success). A total of 4759.9 subject months of follow-up data were analyzed.

The results of the primary safety and effectiveness analyses demonstrated that the pre-specified performance objectives were met and maintained over time. For the cohort described above, the observed freedom from Model 4195 lead related complications at three months was 96.8%, with a 95% lower confidence bound of 94.4% (exceeding the 80% lower bound criterion). The Model 4195 lead observed mean threshold (at 0.5 ms) at three months was 1.3 V, with a 95% upper confidence bound of 1.4 V.

The results of the secondary objectives confirmed that the Model 4195 lead can be successfully and safely implanted. The electrical performance values (e.g., sensing, pacing impedance, etc.) were stable over time and were within expected values, based on Medtronic market-approved LV leads.

### **XI. PANEL RECOMMENDATION**

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In Accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

### **XII. CONCLUSIONS FROM PRECLINICAL AND CLINICAL INVESTIGATIONS**

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Medtronic conducted a hazard analysis on all new features and critical components and then conducted non-clinical laboratory testing as well as clinical testing to evaluate these and other lead features. All test results were found to be acceptable.

The Attain StarFix Model 4195 Lead met both the safety and effectiveness performance criteria and has been determined to be safe and effective for human use. The clinical study of the Medtronic Attain StarFix Model 4195 Lead has shown that the lead performed statistically and clinically acceptable for pacing thresholds and in sensing performance. The lead Model 4195 clinical study also has shown the Model 4195 has acceptable lead handling performance during implant.

The safety and biocompatibility of the Model 4195 lead was evaluated in a series of animal studies. These studies were conducted in accordance with 21 CFR 58 (Good Laboratory Practices) with the exception of the Acute Pass / Pull Beclomethasone Steroid Assay Study, which was found to be acceptable. The results of these tests support the safety and biocompatibility of the Model 4195 lead.

The results of the preclinical and the clinical investigation of the Medtronic Attain StarFix Model 4195 Lead demonstrates that the lead performs according to its design

intent and supports reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use (and directions for use).

### **XIII. CDRH DECISION**

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CDRH issued an approval order on June 13, 2008

The safety and effectiveness of the Medtronic Attain StarFix Model 4195 lead was demonstrated in the results of bench testing, animal studies, and a clinical trial. The Model 4195 lead passed all preclinical tests and had acceptable handling, acceptable pacing and sensing electrical performance, acceptable adverse event rates, and met the predefined safety and effectiveness objective performance criteria. CDRH believes that the sponsor has adequately addressed all of FDA's questions related to the safety and effectiveness of the lead.

The final conditions of approval cited in the approval order are described below.

1. Medtronic will use a 95% of nominal lower limit for batch release assay testing of production leads until either the root cause of the single case of 8% dose variation is found and controls are implemented, or until six consecutive lots of batch release assay testing are found to be consistent with the nominal dose value.
2. Medtronic will collect data for 30 lots or one year, to make an assessment of whether or not the assay (potency) specification can be tightened to 90 – 110% of label claim. Further, Medtronic agrees that if the assay specification can be tightened, the content uniformity requirements for all other dosage forms will follow USP<905>.
3. Medtronic will update the elution specification to at least 80% at the final time point, within 6 months of device approval.
4. Medtronic will conduct a post-approval study to characterize chronic extraction of the Attain StarFix Model 4195 lead. The prospective, non-randomized, controlled study will collect data for 40 extraction attempts of Model 4195 leads at approximately 10 experienced extraction centers for a period of up to 3 years. The study protocol will meet the design elements contained in Medtronic's May 5, 2008 proposal to FDA.
5. Medtronic will conduct a post-approval study to characterize chronic performance of the Attain StarFix Model 4195 lead. The study protocol will meet the design elements contained in Medtronic's May 6, 2008 proposal to FDA including:
  - a. A prospective study design to characterize chronic lead performance following device implant, and will contain a retrospective arm to include subjects from the IDE cohort;
  - b. A post-approval study duration of at least 5 years;

- c. A sample size that results in a 2-sided 95% upper confidence bound of no more than 1.0% for individual adverse event rates, assuming an expected rate of 0.4%, using the exact binomial method;
- d. A total enrollment which accounts for estimated attrition, and an enrollment plan which attempts to fully enroll the study within 24 months of market release, based on current sales estimates;
- e. A primary safety endpoint as complication-free rate greater than 95% at 5 years, with any clinical adverse events omitted from the primary endpoint collected and reported as secondary data;
- f. A rigorous process to monitor the status of all study subjects, to actively follow-up missed visits, and to document the reason for all subject dropouts;
- g. Inclusion of a trend analysis process in the protocol to provide a robust early warning mechanism to identify, characterize, and report adverse events, failure modes, and failure rates;
- h. Post-approval study status reporting at least every 6 months and a mechanism for providing non-scheduled trend analysis reports for new information;
- i. Inclusion of a full list of complications, failure modes, and definition of terms within the study protocol; and
- j. Collection of secondary data including implant data, demographic information, all cause adverse events, electrical performance, returned product analyses, extraction experience, and other parameters of interest.

The applicant's manufacturing facilities were inspected and were found to be in compliance with the Quality System Regulation (21 CFR 820).

#### **XIV. APPROVAL SPECIFICATIONS**

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Directions for Use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.