



Medtronic

ATTAIN ABILITY[®] 4196

Steroid eluting, dual electrode, transvenous, over the wire, cardiac vein pacing lead

DRAFT

Technical Manual

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

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1 Device description

The Medtronic Attain Ability 4196 steroid eluting, dual electrode, transvenous, over the wire, cardiac vein pacing lead is designed for pacing and sensing via a cardiac vein. This lead contains two electrodes: the distal electrode, positioned at the distal tip, and the proximal electrode, positioned 21 mm from the tip. See Section 10.1, "Specifications drawing (nominal)", page 15 for a lead drawing.

The distal tip electrode allows a guide wire to pass through to aid in cardiac vein selection. The distal tip electrode also contains a dual-function steroid-loaded silicone membrane MCRD¹. This membrane seals the lead inner lumen to reduce blood ingress, and the MCRD elutes steroid to reduce inflammatory response within the cardiac vein. The proximal electrode is positioned between the two distal curves of the lead to facilitate contact with the cardiac veins. It also contains an MCRD for elution of steroid. The outer insulation of the lead is polyurethane and the inner insulation is SI-polyimide (SI-PI)². The SI-PI is applied as a coating to the conductor wire prior to coiling. The IS-1 connector pin has a drilled inner lumen to improve guide wire passage³.

The MCRDs contain a combined-total target dosage of 232 µg of dexamethasone acetate. The target dose of the steroid is 160 µg at the tip and 72 µg at the ring of the MCRD. Upon exposure to body fluids, the steroid elutes from the MCRDs. The steroid suppresses the inflammatory response that is believed to cause threshold rise typically associated with implanted pacing electrodes.

The Model 4196 lead can be positioned with the aid of a guide wire or with a stylet. If a stylet is used, use only the stylets packaged with the lead or in a stylet kit (downsized knob). Always use a stylet that is 3 cm (1.2 in) shorter than the lead length listed on the IS-1 connector label.

Note: To implant the Model 4196 lead in a cardiac vein, a compatible delivery system is required. A compatible delivery system includes a guide catheter and either a hemostasis valve or an introducer valve that can be removed or that allows passage over the IS-1 connector. Contact a Medtronic representative for further information regarding compatible delivery systems.

1.1 Package contents

Leads and accessories are supplied sterile. Each package contains the following items:

- 1 lead with anchoring sleeve
- 1 guide wire insertion tool
- 1 guide wire clip
- 1 guide wire steering handle
- extra stylets
- product literature

1.2 Accessory descriptions

Anchoring sleeve – An anchoring sleeve secures the lead to prevent it from moving and protects the lead insulation and conductors from damage caused by tight sutures.

Guide wire clip – A guide wire clip secures the excess guide wire and helps to protect and maintain the sterility of the guide wire.

Guide wire insertion tool – A guide wire insertion tool provides additional control when inserting a guide wire into the lead connector pin or the lead tip.

Guide wire steering handle – A guide wire steering handle is used only with guide wires 0.46 mm (0.018 in) or less in diameter. The steering handle provides additional control and steerability of the guide wire.

Stylet – A stylet provides additional stiffness and controlled flexibility for maneuvering the lead into position. Each stylet knob is labeled with the stylet diameter and length.

2 Drug component description

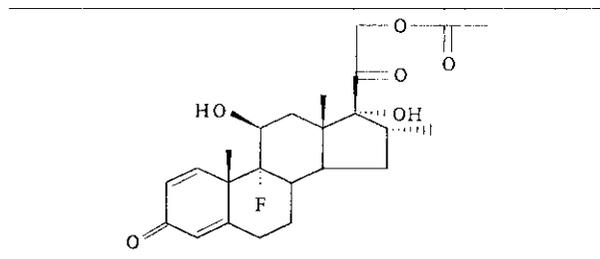
The active ingredient in the Model 4196 lead is dexamethasone acetate. Dexamethasone acetate is 9-Fluoro-11β, 17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-acetate. Dexamethasone acetate has a molecular formula of C₂₄H₃₁FO₅ and a molecular weight of 434.50. The MCRD excipient is silicone. See Figure 1 for the structural formula.

¹ Monolithic controlled release device.

² Technology developed by NASA.

³ IS-1 refers to an International Connector Standard (ISO 5841-3) whereby pulse generators and leads so designated are assured of a basic mechanical fit.

Figure 1.



The target dosage of dexamethasone acetate is 232 µg per lead.

Cautions:

- Drug interactions of dexamethasone acetate with this lead have not been studied.
- Prior to implanting this lead, total patient exposure to dexamethasone acetate should be considered.

3 Indications

The Attain Ability 4196 steroid eluting, dual electrode, IS-1 transvenous lead is indicated for chronic pacing and sensing in the left ventricle via the cardiac vein, when used in conjunction with a compatible Medtronic Cardiac Resynchronization Therapy (CRT) system. Extended bipolar pacing is available using this lead in combination with a compatible CRT-D system and RV defibrillation lead or with a compatible CRT-P system and RV pacing lead.

4 Contraindications

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 232 µg of dexamethasone acetate cannot be tolerated.

5 Warnings and precautions

Bipolar pacing – The Model 4196 was designed for optimal pacing when used in a unipolar or extended bipolar configuration. The standard bipolar configuration may result in markedly elevated pacing thresholds or produce anodal stimulation.

In the event that therapy cannot be delivered via the tip electrode, the ring electrode will be available for use with specific Medtronic devices. Refer to the appropriate CRT-D/CRT-P manual for use with available LV lead pacing configurations with Medtronic CRT devices.

Chronic repositioning or removal – Chronic repositioning or removal of leads may be difficult because of fibrotic tissue development. The clinical study was not designed to evaluate the

removal of left ventricular leads from the coronary venous vasculature. If a lead must be removed or repositioned, proceed with extreme caution. Return all removed leads to Medtronic.

- Rust stylets are not recommended with this lead due to the risk of conductor core/insulation perforation.
- Verify lead length on the IS-1 label on the connector to choose an appropriate stylet kit (downsized knob) length when repositioning. Always choose a stylet kit (downsized knob) 3 cm (1.2 in) shorter than the lead length. For example, choose a stylet kit (downsized knob) with stylets 75 cm long for a lead 78 cm long.
- Lead removal may result in avulsion of the endocardium, valve, or vein.
- Lead junctions may separate, leaving the lead tip and bare wire in the heart or vein.
- Chronic repositioning may adversely affect the low-threshold performance of a steroid eluting lead.
- Cap abandoned leads to avoid transmitting electrical signals.
- For leads that have been severed, seal the remaining lead end and suture the lead to adjacent tissue.
- If a lead is removed and repositioned, inspect it carefully for insulator or conductor coil damage prior to repositioning.

Concurrent devices – Output pulses, especially from unipolar devices, may adversely affect device sensing capabilities. If a patient requires a separate stimulation device, either permanent or temporary, allow enough space between the leads of the separate systems to avoid interference in the sensing capabilities of the devices. Previously implanted pulse generators and implantable cardioverter defibrillators should generally be explanted.

Diathermy – People with metal implants such as pacemakers, implantable cardioverter defibrillators (ICDs), and accompanying leads should not receive diathermy treatment. The interaction between the implant and diathermy can cause tissue damage, fibrillation, or damage to the device components, which could result in serious injury, loss of therapy, and/or the need to reprogram or replace the device.

Handling the guide wire – Handle the guide wire with care at all times.

- Do not insert the proximal end of the guide wire through the lead tip seal without using the guide wire insertion tool. Inserting the guide wire without the guide wire insertion tool could cause damage to the lead tip seal or to the conductor core or insulation.
- Damage to a guide wire may prevent the guide wire from performing with accurate torque response and control and may cause vessel damage. For additional information about vessel damage and other potential adverse events, refer to the technical manual packaged with the appropriate guide wire.

- If the distal end of the guide wire becomes severely kinked or twisted, it may be difficult to withdraw it back through the lead. Therefore, if there is an indication that the distal end of the guide wire has become damaged, or if there is significant resistance in guide wire passage, remove the lead and guide wire together as a unit. Remove the guide wire from the lead and re-insert a new guide wire into the lead. Do not use excessive force to retract the guide wire from the lead. Refer to the product literature packaged with the guide wire for additional information.

Handling the lead – Leads should be handled with care at all times:

- Rust stylets are not recommended with this lead due to the risk of conductor coil or insulation perforation.
- If a stylet is used for lead positioning, use only the stylets packaged with the lead or in a stylet kit (downsized knob). Always use a stylet that is 3 cm shorter than the lead length listed on the IS-1 connector label. Other stylets may extend beyond the lead tip causing lead tip seal damage or injury or perforation of the cardiac vein or heart.
- If the lead is damaged, do not implant it. Return the lead to a Medtronic representative.
- Protect the lead from materials that shed particles such as lint and dust. Lead insulators attract these particles.
- Handle the lead with sterile surgical gloves that have been rinsed in sterile water or a comparable substance.
- Do not severely bend, kink, or stretch the lead.
- Do not use surgical instruments to grasp the lead or connector pin.
- Do not immerse leads in mineral oil, silicone oil, or any other liquid, except blood, at the time of implant.
- Use an anchoring sleeve with all leads. Ensure that the anchoring sleeve is positioned close to the lead connector pin, to prevent inadvertent passage of the sleeve into the vein. If wiping the lead is necessary prior to insertion, ensure that the anchoring sleeve remains in position.
- Do not force the guide catheter or leads if significant resistance is encountered. Use of guide catheters or leads may cause trauma to the heart.

Handling steroid MCRDs⁴ – Avoid reducing the amount of steroid available before implanting the lead. Reducing the available amount of steroid may adversely affect low-threshold performance.

- Do not allow the electrode surfaces to come in contact with surface contaminants.
- Do not wipe or immerse the electrodes in fluid, except blood, at the time of implant.

Steroid use – It has not been determined whether the warnings, precautions, or complications usually associated with injectable dexamethasone acetate apply to the use of this highly localized, controlled-release lead. For a list of potential adverse effects, refer to the *Physicians' Desk Reference*.

Magnetic resonance imaging (MRI) – Do not use magnetic resonance imaging (MRI) on patients who have this device implanted. MRI can induce currents on implanted leads, potentially causing tissue damage and the induction of tachyarrhythmias.

Handling the stylet – Handle the stylet with care at all times.

- To minimize the likelihood of trauma to the vein and to maintain lead flexibility while advancing the lead through the vein, keep the stylet withdrawn 1–2 cm or select a more flexible stylet.
- Do not use excessive force or surgical instruments when inserting a stylet.
- Avoid overbending, kinking, or blood contact on stylets.
- Use a new stylet when blood or other fluids accumulate on the stylet. Accumulated fluids may cause damage to the lead or difficulty in passing the stylet through the lead.
- Curving the distal end of the stylet prior to insertion into the lead will achieve a curvature at the distal end of the lead. Do not use a sharp object to impart a curve to the distal end of the stylet.

Inspecting the sterile package – Inspect the sterile package with care before opening it.

- Contact a Medtronic representative if the seal or package is damaged.
- Store at 25 °C (77 °F). Excursions from this storage temperature are permitted in the range of 15 to 30 °C (59 to 86 °F). (See USP Controlled Room Temperature.) According to USP excursion conditions, transient spikes up to 40 °C (104 °F) are permitted as long as they do not exceed 24 hours.
- Do not use the product after its expiration date.

Single use – The lead is for single use only.

Sterilization – Medtronic has sterilized the package contents with ethylene oxide before shipment. This lead is for single use only and is not intended to be resterilized.

Line-powered and battery-powered equipment – An implanted lead forms a direct current path to the myocardium. During lead implant and testing, use only battery-powered equipment or line-powered equipment specifically designed for this purpose to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

Necessary hospital equipment – Keep external defibrillation equipment nearby for immediate use during acute lead system testing, the implant procedure, or whenever arrhythmias are possible or intentionally induced during post-implant testing. Backup pacing should be readily available during implant. Use of the delivery system or leads may cause heart block.

⁴ Monolithic controlled release device

6 Potential adverse events

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

- Air embolism
- Avulsion or other damage to the endocardium, valve, or vein (particularly in fragile hearts)
- Cardiac dissection or perforation
- Cardiac tamponade
- Coronary sinus dissection
- Death
- Endocarditis or pericarditis
- Erosion through the skin
- Extracardiac muscle or nerve stimulation
- Fibrillation or other arrhythmias
- Heart block
- Heart wall or vein wall rupture
- Hematoma/seroma
- Infection
- Lead conductor fracture or insulation failure
- Lead dislodgement
- Myocardial irritability
- Myopotential sensing
- Pericardial effusion or rub
- Pneumothorax
- Rejection phenomena (local tissue reaction, fibrotic tissue formation)
- Threshold elevation or exit block
- Thrombosis
- Thrombotic embolism

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	Corrective action to be considered
Lead dislodgement ^a	Intermittent or continuous loss of capture or sensing ^a	Reposition the lead.
Lead dislodgement ^a	Intermittent or continuous oversensing	Reposition the lead.
Lead conductor fracture or insulation failure	Intermittent or continuous loss of capture or sensing ^a	Replace the lead.
Threshold elevation or exit block	Loss of capture ^a	Adjust the implantable device output. Replace or reposition the lead.

^a Transient loss of capture or sensing may occur following surgery until lead stabilization takes place. If stabilization does not occur, lead dislodgement may be suspected.

Implant techniques that may damage the lead include, but are not limited to, the following:

Implant techniques that may damage the lead	Possible effects on the lead	Corrective action to be considered
Forcing the lead through the introducer/delivery system	Electrode, conductor coil, and/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.
Using too stiff a stylet	Conductor coil/insulation perforation	Replace the lead.
Puncturing the periosfeum and/or tendon when using subclavian introducer approach	Conductor coil fracture, insulation damage	Replace the lead.
Advancing the lead through the veins without the stylet or guide wire fully inserted	Tip distortion and/or insulation perforation	Replace the lead.
Inserting the proximal end of the guide wire through the lead tip seal without using the guide wire insertion tool	Lead tip seal damage and/or conductor coil/insulation damage	Replace the lead.
Advancing a stylet tip beyond the distal end of the lead tip seal	Lead tip seal damage	Replace the lead.

7 Drug Information

7.1 Steroid mechanism of action

Steroid suppresses the inflammatory response that is believed to cause threshold rises typically associated with implanted pacing electrodes. Glucocorticoids decrease inflammation by stabilizing leukocyte lysosomal membranes. The membrane stabilization prevents the release of destructive acid hydrolases for the leukocytes and this inhibits the accumulation of macrophages in the inflamed area. The mechanism involves the activation of glucocorticoid receptors that increase or decrease the transcription of a number of genes involved in the inflammatory process. One of the key actions is the repression of cytokine gene transcription and other transcription factors activated in chronic inflammation.

7.2 Pharmacokinetics of leads using dexamethasone acetate steroid

Pharmacokinetics – The pharmacokinetics (local drug levels and systemic levels) of dexamethasone acetate and its metabolites following implant were not evaluated in human clinical trials. When delivered intra-muscularly, the lipid-soluble

dexamethasone acetate is slowly absorbed throughout the tissue.

Metabolism – The conversion of dexamethasone acetate to dexamethasone occurs within hours. The dexamethasone alcohol (dexamethasone) is the active glucocorticoid used in this Medtronic lead. Steroid is applied via MCRD (Monolithic controlled release device) and eluted to the tissue interface where it will be used. The form of the steroid, whether it is a prodrug or the pharmacologically active dexamethasone, is irrelevant, as the steroid is directly present at the injury site to treat the inflammation. Dexamethasone acetate is hydrolyzed into dexamethasone, which is readily absorbed by the surrounding tissue and body fluids. Glucocorticoids, when given systemically, are eliminated primarily by renal excretion of inactive metabolites.

7.3 Mutagenesis, carcinogenicity, and reproductive toxicity

The mutagenesis, carcinogenicity, and reproductive toxicity of the Model 4196 lead have not been evaluated. However, the mutagenesis, carcinogenicity, and reproductive toxicity of dexamethasone acetate have previously been evaluated.

Mutagenesis – Genotoxicity evaluation of dexamethasone was undertaken using *in vitro* and *in vivo* assays. Analyses of chromosomal aberrations, sister-chromatid exchanges in human lymphocytes, and micronuclei and sister-chromatid exchanges in mouse bone marrow showed dexamethasone to be capable of attacking the genetic material. However, the Ames/Salmonella assay, both with and without S9 mix, did not show any increase His+ revertants.

Carcinogenicity – Although adequate and well-controlled animal studies have not been performed on Dexamethasone acetate, use in humans has not shown an increase in malignant disease.

Reproductive Toxicity – Adrenocorticoids have been reported to increase or decrease the number and motility of spermatozoa. However, it is not known whether reproductive capacity in humans is adversely affected.

Pregnancy – Adrenocorticoids cross the placenta. Although adequate studies have not been performed in humans, there is some evidence that pharmacologic doses of adrenocorticoids may increase the risk of placental insufficiency, decreased birth weights or stillbirth. However, teratogenic effects in humans have not been confirmed.

Infants born to mothers who have received substantial doses of adrenocorticoids during pregnancy should be carefully observed for signs of hypoadrenalism and replacement therapy administered as required.

Prenatal administration of dexamethasone to the mother to prevent respiratory distress syndrome in the premature neonate has not been shown to affect the child's growth or development adversely. Physiologic replacement doses of adrenocorticoids administered for treatment of adrenal insufficiency are also unlikely to adversely affect the fetus or neonate. Animal studies have shown that adrenocorticoids increase the instance of cleft

palate, placental insufficiency, spontaneous abortions, and intrauterine growth retardation.

Lactation – Problems in humans have not been documented. Adrenocorticoids are excreted in breast milk and may cause unwanted defects such as growth suspension and inhibition of endogenous steroid production in the infant.

8 Adverse events and clinical trial data

Information regarding the Model 4196 lead clinical study and adverse events is available at www.medtronic.com/manuals. To view, download, print, or order the clinical study from the Medtronic website:

1. Navigate your web browser to www.medtronic.com/manuals.
2. Set the "Your Location" option to United States and click [OK].
3. Select the "Search for:" field on the left side of the screen and type "4196."
4. Click [Search]. All technical literature for this lead will be listed.

If you do not have web access, a printed copy of the Model 4196 Clinical Study Summary can be obtained from your Medtronic representative or call the toll-free number located on the back cover.

9 Directions for use

Warning: Do not force the guide catheter or leads if significant resistance is encountered. Use of guide catheters and or leads may cause trauma to the heart.

Note: To implant the Model 4196 lead in a cardiac vein, a compatible delivery system is required, such as a Medtronic delivery system. A compatible delivery system includes a guide catheter and a hemostasis valve or introducer valve which allows passage through or removal from an IS-1 connector. Contact a Medtronic representative for further information regarding compatible delivery systems.

Proper surgical procedures and sterile techniques are the responsibility of the medical professional. The implant procedures described in this manual are provided for information only. Each physician must apply the information in these instructions according to professional medical training and experience.



Medtronic

ATTAIN ABILITY[®] 4196 LEFT VENTRICULAR LEAD

Clinical study information and adverse events

Clinical study

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

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Medtronic

Alleviating Pain · Restoring Health · Extending Life

**Attain Ability[®] Model 4196 Left Ventricular Lead
Summary of Clinical Results**

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Please see the Technical Manual for a complete device description, indications for use, contraindications, warnings and precautions, drug information, potential adverse events, and directions for use. The Technical Manual is available at www.Medtronic.com/manuals. To view, download, print, or order the Technical Manual from the Medtronic website:

- 1. Navigate your web browser to <http://www.Medtronic.com/manuals>.*
- 2. Set the "Your Location" option to United States and click [OK].*
- 3. Select the "Model # or Name" field on the left side of the screen and type "4196".*
- 4. Click [Search]. All technical literature for this lead will be listed.*
- 5. Select the Technical Manual from the technical literature.*

Summary of Clinical Results

Study Title: The Attain Ability® Model 4196 Left Ventricular Lead Clinical Study

Number of Centers: 20 US and 5 Canada

Number of Subjects: 149 subjects enrolled, 135 subjects implanted with a Medtronic Model 4196 lead

1 Study Purpose

The purpose of the clinical study was to assess the safety and efficacy of the Medtronic Attain Ability® Model 4196 lead.

2 Study Scope, Design, and Methods

This was a prospective, multi-center (up to 20 US and 5 Canada) clinical trial using objective performance criteria (OPC) to evaluate the safety and efficacy of the Model 4196 left ventricular (LV) lead. Data from previous LV lead studies were used to establish the Model 4196 lead OPC. 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 4196 lead implant were evaluated at pre-hospital discharge, one month, three months, six months, and every six months thereafter, until study completion. Data was collected via case report forms, programmer strips and save-to-disk files.

A total of 149 subjects were enrolled, 135 of which were successfully implanted with a Model 4196 lead. There were 110 subjects enrolled and 98 subjects implanted with the Model 4196 lead at 17 centers in the US and 39 subjects enrolled and 37 subjects implanted with the Model 4196 lead at 5 centers in Canada.

3 Subject Inclusion and Exclusion Criteria

Subjects of both genders who were indicated for CRT-D and who met all inclusion and no exclusion criteria were eligible for a Model 4196 lead implant attempt.

3.1 Inclusion Criteria

- Subject has a demonstrated prolonged QRS defined as an intrinsic QRS duration \geq 120 ms (test documented within six months of Baseline)
- Subject has a left ventricular ejection fraction (LVEF) \leq 35% (test 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 implantable cardioverter (ICD) that precludes waiting for the one month or three months medication requirement for an ACE inhibitor, ARB, or beta-blocker

- Subject is indicated for ICD implantation for the treatment of life-threatening ventricular arrhythmias¹
- Subject has signed and dated the study-specific informed consent form
- 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 protocol

3.2 *Exclusion Criteria*

- Subject has a previous complete atrial-based biventricular CRT system
- Subject has a previous LV lead implanted or previous lead implant attempt within 30 days of implant or ongoing AEs from previous unsuccessful attempt
- Subject has unstable angina pectoris or has had an acute myocardial infarction (MI) within the past month
- Subject has had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past three months
- Subject has chronic (permanent) atrial arrhythmias
- Subject has contraindications for standard transvenous cardiac pacing (e.g., mechanical right heart valve)
- Subject has had a heart transplant (subjects waiting for heart transplants are allowed in the study)
- Subject is contraindicated for < 1 mg dexamethasone acetate
- Subject is enrolled in any concurrent drug and/or device study that may confound the results of this study
- Subject has a terminal illness and is not expected to survive more than three months
- Subject is a woman who is pregnant or has child-bearing potential and is not on a reliable form of birth control (pregnancy test required within seven days prior to implant for female patients with child bearing potential)
- Subject is unable to tolerate an urgent thoracotomy

¹ In accordance with Class I or II ICD indications as specified in the current ACC/AHA/HRS practice guidelines at the time of implant.

4 Study Objectives

4.1 Primary Objectives

There were three primary study objectives for the Model 4196 lead clinical study.

4.1.1 Safety

The Model 4196 lead will be considered safe if its complication-free rate at the end of the one month follow-up window is greater than 80%.

4.1.2 Efficacy

The distal tip electrode of the Model 4196 lead will be considered effective if the mean left ventricular (LV) voltage threshold (at 0.5ms) at the one month visit using the tip electrode is less than 3.0 volts.

The proximal ring electrode of the Model 4196 lead will be considered effective if the mean left ventricular voltage threshold (at 0.5 ms) at the three month visit using the ring electrode is less than 4.0 volts.

4.2 Secondary Objectives

- To characterize the LV voltage thresholds, LV sensing and LV pacing impedance of the Model 4196 lead tip electrode at implant and follow-up.
- To characterize the LV voltage thresholds, LV sensing (implant only) and LV pacing impedance of the Model 4196 lead ring electrode at implant and follow-up.
- To evaluate the implant success rates of the Model 4196 lead and the Attain family of leads.
- To evaluate the following implant-related times: total implant, fluoroscopy, coronary sinus (CS) cannulation, and placement of the Model 4196 lead.
- To characterize all adverse events (AE), excluding unavoidable AEs.
- To evaluate the Model 4196 lead handling characteristics such as pushability, steerability, and stability.

5 Results

The clinical study for the Medtronic Attain Ability® Model 4196 lead was approved for 150 subjects at up to 20 centers in the US on March 2, 2007. Medtronic also collected data for up to 50 subjects at 5 centers in Canada. Per the clinical investigational plan, the primary safety and effectiveness objectives were evaluated when the study's critical sample size was met.

Subject data that occurred by August 20, 2007 and received by Medtronic by September 4, 2007 are summarized. Updates to the data were allowed until final database closure of September 14, 2007. Note at the time of the PMA analysis the clinical study was ongoing. The last subject was implanted in the Model 4196 clinical study on Sept 24, 2007, and this additional implant and follow-up experience was summarized at a later date in a progress report¹.

5.1 Subject Demographics

The demographics for this cohort are presented in Table 1. Subjects ranged in age from 33.0 to 86.7 years, with a mean age of 68.7 years. One hundred and ten (110) of the subjects (75.3%) were male and 36 of the subjects (24.7%) were female. The majority of subjects were NYHA Class III (144, 98.6%) and the remaining patients were NYHA Class IV (2, 1.4%). The subject cohort had a mean intrinsic QRS width of 151.8 ms (SD = 24.5) and a mean LV ejection fraction of 23.9% (SD = 6.9). The majority of subjects were an ethnic origin of white (88.4%) and had an ICD Indication of Left Ventricular Ejection Fraction <35% with NYHA Class II or III, regardless of etiology (75.3%).

Category	Subjects with implant attempt (N = 146)¹
Gender, N (%)	
Male	110 (75.3%)
Female	36 (24.7%)
Age (years)	
Mean	68.7
Standard deviation	11.7
Range	33.0-86.7
NYHA functional classification, N (%)	
Class III	144 (98.6%)
Class IV	2 (1.4%)
Primary Inclusion Criteria Values	
LV Ejection Fraction (mean %)	23.9
Intrinsic QRS Width (mean ms)	151.8
Pre-existing IPG/ICD Status	
None	99 (67.8%)
ICD	33(22.6%)
IPG	14 (9.6%)

¹ Subjects who underwent an implant attempt (incision made) were included in the study population analysis.

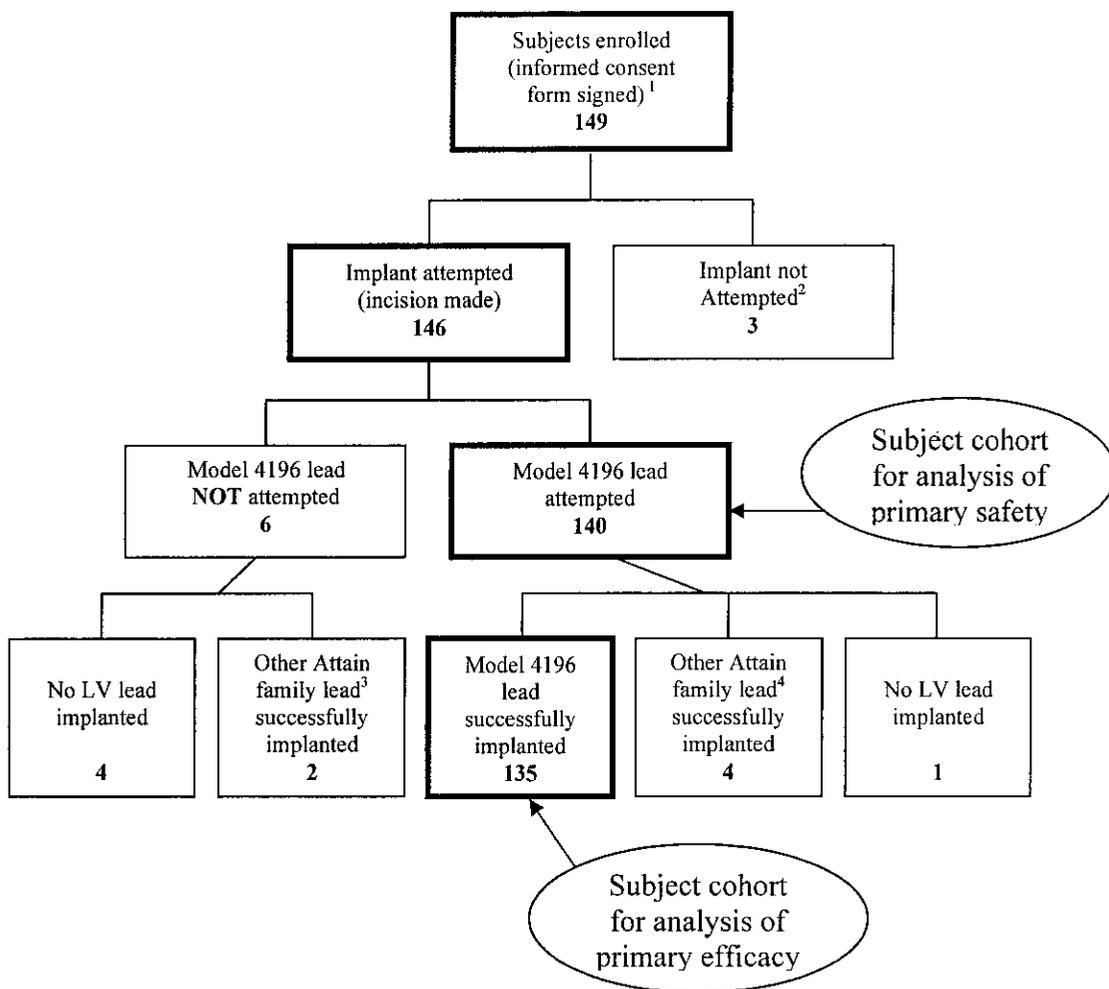
¹ Attain Ability Model 4196 Left Ventricular Lead FDA Annual Progress Report, Version 1, 27 Feb 2008

5.2 Procedure Summary

Per the clinical investigational plan, if a 4196 lead was implanted, the required system was to include a market released right atrial lead and a market released Medtronic right ventricular lead. In addition, the implanted system had to include a Medtronic market released CR device which can be programmed to utilize both electrodes, i.e. Concerto® Model C154DWK or Concerto-AT C174AWK. If the Model 4196 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.

A summary of enrollment status is presented in Figure 1. Of the 149 subjects enrolled, 146 underwent an implant attempt, with 140 undergoing a Model 4196 lead implant attempt. Of the 140 subjects who had a Model 4196 lead implant attempt, 135 (96.4%) had a successful Model 4196 lead implant. All implant success rates were within the expected range for Medtronic LV lead implants.

Figure 1: Enrollment Status



¹ Adverse events are reported for all subjects enrolled through the time of exit.

² Two subjects did not meet inclusion/exclusion criteria after signing the informed consent. One subject was exited prior to implant because the physician opted for a different treatment for patient.

³ The "Other Attain family leads" implanted in the subjects not attempted with the Model 4196 lead were both Model 4194 leads.

⁴ The "Other Attain family leads" implanted in the subjects attempted with the Model 4196 lead were two Model 4194 leads, one Model 4193 lead, and one Model 4195 lead (in Canada).

After successful cannulation of the coronary sinus, five subjects who were attempted with a Model 4196 lead implant were not successfully implanted with a Model 4196 lead. Table 2 presents the reasons for the unsuccessful Model 4196 lead implant attempts.

Table 2: Unsuccessful Model 4196 lead implant attempts (N=5)	
Reason	Number (not mutually exclusive)
Unable to access coronary vein	1
Dislodgement/Unstable location	3
Dislodged during slitting	3
Phrenic nerve/diaphragmatic stimulation	1
Wanted to engage another vein	1
Tip of 4196 not large enough to secure in distal vein	3
Used sub selecting inner-catheter to guide wire sub-branch which caused unsuccessful attempt	1

5.3 Follow-up Experience

This summary includes 216.9 device months of experience. Subject follow-ups ranged from 0 to 6.2 months and averaged 1.5 ± 1.3 months (median = 1.2 months).

5.4 Primary Objectives

A summary of the primary objectives is presented in Table 3.

Table 3: Summary of Primary Objectives	
Primary Objective	Results
Safety: The Model 4196 lead will be considered safe if its complication-free rate at the end of the one month follow-up window is greater than 80%	Observed complication-free rate from Model 4196 lead related complications at one month = 95.3% One-sided 95% confidence interval lower bound = 90.3% (6 Model 4196 complications in 5 subjects) Performance Objective Met
Effectiveness: The distal tip electrode of the Model 4196 lead will be considered effective if the mean LV voltage threshold (at 0.5 ms) at the one month visit using the tip electrode is less than 3.0 volts	Observed mean Model 4196 LV tip electrode voltage threshold at one month = 1.1 V One-sided 95% confidence interval upper bound = 1.2 V Performance Objective Met
Effectiveness: The proximal ring electrode of the Model 4196 lead will be considered effective if the mean LV voltage threshold (at 0.5 ms) at the three month visit using the ring electrode is less than 4.0 volts	Observed mean Model 4196 LV ring electrode voltage threshold at three months = 1.8 V One-sided 97.5% confidence interval upper bound = 2.3 V Performance Objective Met

5.4.1 Safety objective

The safety of the Model 4196 lead was evaluated by investigator documentation of all Model 4196 lead related adverse events. All subjects with a Model 4196 lead attempt were included in this evaluation.

Of the 146 subjects who underwent an implant attempt, 140 subjects underwent a Model 4196 lead attempt and are included in the safety endpoint. Among the 105 subjects who completed a one month follow-up or a later follow-up, 101 subjects did not experience any Model 4196 lead related complications. One additional subject did not complete their one month follow-up; however, a Model 4196 related complication was observed prior to their one month visit window cut-off date. Since documentation of the complication was complete and valid, this complication was considered confirmed and reportable, hence included in the primary endpoint analysis (i.e. the patient was included in the denominator of the analysis and the complication was counted against the numerator). Freedom from lead related complications at one month are presented in Table 4.

Table 4: Freedom from Model 4196 lead related complications at one month				
Number of Subjects ¹	Number of subjects with events (cumulative)	Observed complication-free rate	95% lower confidence bound (one-sided)	Predetermined Acceptance Criteria
106	5	95.3%	90.3%	80%

¹ Includes all subjects who completed a one month follow-up or a later follow-up, or experienced a Model 4196 lead related complication within one month follow-up window

At one month, the primary objective end point, five subjects had experienced a total of six Model 4196 lead related complications. Table 5 presents the Model 4196 lead related complications and treatments.

Table 5: Treatment of Model 4196 lead related complications through one month		
Event (Six events in five subjects)	Treatment	N
Lead dislodgement	Lead repositioned	3
	Lead replaced ¹	2
	LV lead programmed off ²	1

¹ One subject had the Model 4196 lead replaced with a Model 4194 lead and a second subject had it replaced with a Model 4193 lead.

² One subject was awaiting LV lead repositioning at the time of the visit cut-off date.

5.4.2 Efficacy objective

Table 6 and Table 7 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. Unable-to-capture (UTC) thresholds were not included in the efficacy analysis but were included as lead related adverse events if UTC at both electrodes at maximum output. All subjects who were reported as UTC were able to capture using the alternate electrode unless footnoted.

Visit	UTC	N	Mean (volts)	Median	Std. Dev.	Range	95% UCB
Implant	0	135	1.0	0.6	0.9	0.2 - 6.2	1.1
Pre-hospital discharge	1 ¹	125	1.2	0.5	1.2	0.5 - 8.0	1.3
1 month	1¹	99	1.1²	1.0	0.8	0.5 - 5.0	1.2
3 month	0	50	1.0	1.0	0.7	0.5 - 3.0	1.1
6 month	0	1	1.0	1.0	-	1.0 - 1.0	-

¹ Two subjects were unable to capture at both electrodes and LV lead dislodgements were confirmed.

² Exceeds acceptance criteria of 3.0V.

Visit	UTC	N	Mean (volts)	Median	Std. Dev.	Range	97.5% UCB
Implant	8	126	1.8	0.9	1.9	0.3 - 9.9	2.1
Pre-hospital discharge	12 ¹	112	2.2	1.0	2.1	0.5 - 8.0	2.5
1 month	10 ¹	88	2.0	1.0	2.0	0.5 - 8.0	2.3
3 month	8	42	1.8²	1.0	2.0	0.5 - 8.0	2.3
6 month	1	0	-	-	-	-	-

¹ Two subjects were unable to capture at both electrodes and LV lead dislodgements were confirmed.

² Exceeds acceptance criteria of 4.0V.

With the dual electrode design, the Model 4196 lead provides the physician a second option to pace the LV. Table 8 summarizes the pacing configuration selected at implant and the start of each follow-up visit. Table 9 summarizes the voltage threshold for the permanently programmed pacing configuration.

Visit	N	LVtip to RVcoil	LVring to RVcoil	Other
Implant	135	103 (76.3%)	30 (22.2%)	2 (1.5%) ¹
Pre-hospital discharge	133	101 (75.9%)	29 (21.8%)	3 (2.3%) ²
One month	101	73 (72.3%)	26 (25.7%)	2 (2.0%) ³
Three month	50	35 (70.0%)	15 (30.0%)	0 (0.0%)
Six month	1	1 (100%)	0 (0.00%)	0 (0.0%)

¹ Two subjects were programmed to the bipolar (LV tip/LV ring) configuration.

² Two subjects were programmed to the bipolar (LV tip/LV ring) configuration. One subject had the LV lead programmed off following the implant, but prior to the pre-hospital discharge visit.

³ One subject was programmed to the bipolar (LV tip/LV ring) configuration. One subject had the LV lead programmed off due to dislodgement.

Visit	UTC	N	Mean (volts)	Median	Std. Dev.	Range
Implant	0	135	0.9	0.6	0.8	0.3 - 4.5
Pre-hospital discharge	1 ¹	125	1.1	0.5	1.0	0.5 - 6.0
One month	1 ¹	99	1.1	1.0	0.8	0.5 - 5.0
Three month	0	50	1.0	0.5	0.7	0.5 - 3.0
Six month	0	1	1.0	1.0	-	1.0 - 1.0

¹ Two subjects are listed as UTC at the permanently programmed configuration and LV lead dislodgements were confirmed.

In the Model 4196 clinical study there were 10 adverse events (in 9 subjects) reported for extracardiac stimulation caused by LV pacing (see table 10 below). There were no subjects that required surgical intervention in order to eliminate the extracardiac stimulation while maintaining biventricular pacing, so all ten of the events were classified as observations. Three of the events were treated by utilizing an alternate electrode configuration and seven of the events were treated by changing the pacing output.

Table 10: Events Related to LV Pacing and Programming Treatment		
Adverse Event	Number of Events (subjects)	Treatment (number of events)
Chest wall stimulation	1 (1)	Changed pacing output (1)
Possible chest wall stimulation	1 (1)	Changed pacing output (1)
Muscle stimulation-diaphragm	8 (7)	Utilized an alternate configuration (3)
		Changed pacing output (5)

In addition to the 10 events described above related to LV pacing, there were 6 adverse events (in 5 subjects) reported for LV lead dislodgement. For each of these subjects there was visual evidence, e.g. Chest X-ray or fluoroscopy, which confirmed a lead dislodgment that necessitated additional treatment beyond reprogramming. Therefore, the six LV lead dislodgments were all classified as complications because they resulted in invasive intervention or termination of significant device function (see table 5 above).

5.5 Secondary Objectives

The secondary objectives examined the Attain lead family and Model 4196 lead implant success, lead placement and procedure time, lead handling, additional electrical performance, and all adverse events reported in the study. Table 11 presents a summary of the secondary objectives results, with the exception of adverse events, which are presented in the *Adverse Events Summary* section.

Table 11: Summary of Secondary Objectives Results	
Secondary objective	Results
Evaluate the Attain leads implant success	All transvenous LV leads success = 96.6% (141/146) All transvenous LV leads success after cannulation = 98.6% (141/143) Attain family success = 96.6% (141/146) Model 4196 lead success = 96.4% (135/140)
Evaluate total implant, fluoroscopy, cannulation, and Model 4196 lead placement time (mean ± standard deviation)	Cannulation time = 11.5 min ± 4.0 Fluoroscopy time = 25.6 min ± 18.3 Model 4196 lead placement time = 12.2 min ± 10.0 Total implant time = 119.2 min ± 104.0
Evaluate lead handling	Ability to Push (Good or Fair) = 98.5% (135/137) Ability to Navigate (Good or Fair) = 99.3% (138/139) Stability at final location (Good or Fair) = 94.2% (131/139) Stability while slitting (Good or Fair) = 97.8% (136/139) Acceptability = 98.6% (137/139)
Characterize the electrical performance of the Model 4196 LV lead tip electrode (Mean ± standard deviation) <ul style="list-style-type: none"> • LV R-wave amplitude • LV lead impedance • LV Voltage thresholds measured at 0.5 ms 	Model 4196 Lead Electrical Performance at Implant <ul style="list-style-type: none"> • R-Wave Amplitude = 17.1 mV ± 7.1 (N = 129) • Impedance = 674.1 Ohms ± 217.2 (N = 135) • Voltage Threshold = 1.0 V ± 0.9 (N = 135) Model 4196 Lead Electrical Performance at Discharge <ul style="list-style-type: none"> • R-Wave Amplitude = 16.7 mV ± 5.7 (N = 127) • Impedance = 494.4 Ohms ± 168.4 (N = 130) • Voltage Threshold = 1.2 V ± 1.2 (N = 125) Model 4196 Lead Electrical Performance at One month <ul style="list-style-type: none"> • R-Wave Amplitude = 17.6 mV ± 6.3 (N = 97) • Impedance = 496.4 Ohms ± 128.5 (N = 98) • Voltage Threshold = 1.1 V ± 0.8 (N = 99) Model 4196 Lead Electrical Performance at Three months <ul style="list-style-type: none"> • R-Wave Amplitude = 17.8 mV ± 6.2 (N = 48) • Impedance = 519.4 Ohms ± 170.5 (N = 50) • Voltage Threshold = 1.0 V ± 0.7 (N = 50)
Characterize the electrical performance of the Model 4196 LV lead ring electrode (Mean ± standard deviation) <ul style="list-style-type: none"> • LV R-wave amplitude (implant only) • LV lead impedance • LV Voltage thresholds measured at 0.5 ms 	Model 4196 Lead Electrical Performance at Implant <ul style="list-style-type: none"> • R-Wave Amplitude = 15.3 mV ± 6.9 (N = 129) • Impedance = 588.3 Ohms ± 246.3 (N = 135) • Voltage Threshold = 1.8 V ± 1.9 (N = 126) Model 4196 Lead Electrical Performance at Discharge <ul style="list-style-type: none"> • Impedance = 399.0 Ohms ± 94.2 (N = 128) • Voltage Threshold = 2.2 V ± 2.1 (N = 112) Model 4196 Lead Electrical Performance at One month <ul style="list-style-type: none"> • Impedance = 509.1 Ohms ± 309.9 (N = 98) • Voltage Threshold = 2.0 V ± 2.0 (N = 88) Model 4196 Lead Electrical Performance at Three months <ul style="list-style-type: none"> • Impedance = 515.4 Ohms ± 315.7 (N = 50) • Voltage Threshold = 1.8 V ± 2.0 (N = 42)

5.6 Adverse Events Summary

For the purpose of the Model 4196 lead study, an adverse event was defined as any undesirable clinical occurrence in a subject, whether or not related to the investigational device. The center categorized adverse events by event code, 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. All adverse events were adjudicated by the Adverse Events Advisory Committee (AEAC) based on the event code, relatedness, and complication/observation. 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 CRT system, implant tools, therapy, or procedure.

A total of 132 adverse events were reported in the subject cohort and are presented in Table 12. Thirty eight (28.8%) of the events were classified as complications and 94 (71.2 %) were classified as observations.

Table 12 provides a summary of all adverse events by relatedness. Incidence rate per subject month were calculated by dividing the number of events by the total time (months) when subjects were exposed to the risk for having an event. The subject cohort for left ventricular lead related events were subjects who underwent a Model 4196 implant attempt; the subject cohort for right ventricular lead related events, cardiac resynchronization device related events, cardiac resynchronization system related events, implant tool related events and implant procedure related events were subjects who underwent an implant attempt; the subject cohort for not cardiac resynchronization system related events were all subjects enrolled in this study. Tables 12 through 14 summarize all adverse events that were Model 4196 LV lead related (Table 13), implant procedure related (Table 14), and implant tool related (Table 15). Incidence rate for these tables were determined by dividing the total number of subjects with each event by the number of subjects at risk (N) for that event.

Table 12: Summary of All Adverse Events				
Relatedness	Complications		Observations	
	Number of Events	Incidence Rate (event per subject month)	Number of Events	Incidence Rate (event per subject month)
Left ventricular lead	6	0.0277	10	0.0461
Right ventricular lead	2	0.0090	2	0.0090
Cardiac resynchronization device	0	0.0000	3	0.0136
Cardiac resynchronization system	0	0.0000	2	0.0090
Implant tool	1	0.0045	5	0.0226
Implant procedure	2	0.0090	8	0.0362
Not cardiac resynchronization system related	27	0.1182	64	0.2802
Total	38	0.1664	94	0.4116

Table 13: LV lead related adverse events: Model 4196 lead (N = 140)				
Event	Complications	Observations	Number of subjects	Percent of Subjects with Event (%)
Chest wall stimulation	0	1	1	0.7
Possible chest wall stimulation	0	1	1	0.7
Lead dislodgement	6	0	5	3.6
Muscle stimulation-diaphragm	0	8	7	5.0
Total	6	10	14	10.0

Table 14: Implant procedure related adverse events (N = 146)				
Event	Complications	Observations	Number of subjects	Percent of Subjects with Event (%)
Lead not fully inserted in header	1	0	1	0.7
Pocket site ecchymosis	0	1	1	0.7
Atrial fibrillation	0	1	1	0.7
Intraoperative bleeding	0	1	1	0.7
Pocket infection	0	2	2	1.4
Pocket seroma/hematoma	1	2	3	2.1
Swelling at pocket site	0	1	1	0.7
Total	2	8	9	6.2

Table 15: Implant tool related adverse events (N = 146)				
Event	Complications	Observations	Number of subjects	Percent of Subjects with Event (%)
Cardiac perforation	1	0	1	0.7
Cardiac vein dissection	0	3	3	2.1
Coronary sinus dissection	0	1	1	0.7
Coronary sinus perforation	0	1	1	0.7
Total	1	5	5	3.4

5.7 Death summary

As of August 20, 2007, two subjects had exited the Model 4196 LV lead study due to death. The AEAC classified one death as non-cardiac related, non-sudden and witnessed. The second death was classified as unknown cause and non-witnessed. Neither of the subject deaths was thought to be LV lead related.

5.8 Poolability and Gender Analysis

The Model 4196 Clinical Study included data from multiple centers with centralized coordination, data processing and reporting to Medtronic. All of the clinical centers followed the requirements of an identical protocol and all of the clinical centers used the same methods to collect and report the clinical data.

Poolability analyses by gender were conducted for all primary endpoints:

- Lead Complication (1 month)
- Tip electrode threshold (1 month)
- Ring electrode threshold (3 month)

The poolability analyses by gender determined that there is no significant difference in the primary safety and the ring electrode efficacy endpoint between men and women. The female cohort reported a statistically significantly higher tip threshold as compared to the men (p-value = 0.041) however the mean threshold for both groups is well below the pre-specified objective performance criteria (3.0V @ 0.5msec). The poolability analysis results support that the Model 4196 Lead is safe and effective for both genders



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