SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Names: Pump, Infusion, Implanted, Programmable
Implantable Intravascular Catheter
Clinician Programmer

Device Trade Names: Implantable System for Remodulin®

Device Procode: LKK

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

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Numbers: P140032

Date of FDA Notice of Approval: 12/22/2017

Priority Review: No

II. INDICATIONS FOR USE

The Implantable System for Remodulin® is indicated for adult patients with Class I, II and III pulmonary arterial hypertension (PAH) receiving intravenous delivery of Remodulin.

Physicians prescribing this system for use with Remodulin must be familiar with the indications, contraindications, warnings, precautions, adverse events, and dosage and administration information described in the Remodulin drug labeling.

The Model 8551 Refill Kit is intended for use in refilling the Medtronic implantable programmable infusion pumps with the exception of Medtronic MiniMed infusion pumps.

III. CONTRAINDICATIONS

Contraindications for the Implantable System for Remodulin® are listed by category:

System implantation – Implantation of the system is contraindicated:

- for NYHA Class IV PAH patients

- in the presence of known or suspected infections, bacteremia, or sepsis requiring antibiotics
- for patients with vasculature that is inadequate for an 8 French introducer or catheter advancement without stylet guidance
- when the pump cannot be implanted 2.5 cm or less from the surface of the skin
- where skin or soft tissue would heal poorly, increase susceptibility to infections, or is unacceptable for implant of this system
- for patients implanted with leads or catheters (active or abandoned) in the superior vena cava that cannot be removed prior to or at system implant
- for patients who cannot safely tolerate sudden interruptions in treatment.
- in patients whose body size is not sufficient to accept pump bulk and weight

Remodulin – Limited to use with of Remodulin (10 mg/ml concentration). All other drugs are contraindicated. Contraindications relating to the use of Remodulin must be observed.

Blood sampling – Blood sampling or aspiration through the catheter access port is contraindicated.

Catheter access port kits – Medtronic catheter access port kits are contraindicated for use with the Implantable System for Remodulin®.

Refill kits – Medtronic refill kits are contraindicated for all catheter access port procedures.

Anticoagulation – Implant of the infusion system is contraindicated if anticoagulation therapy cannot be managed.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Implantable System for Remodulin® labeling

a. During the pivotal clinical trial for the Implantable System for Remodulin®, 10% of patients experienced pump failures after 4 years of use. At least 33% of these failures occurring after four years of use resulted in the device failing to deliver Remodulin without corresponding error alarm. The remaining percentage of reported malfunctions occurred with a motor stall alarm that was reported by the patient. Patients who cannot tolerate a sudden cessation of Remodulin therapy may not be appropriate candidates for the Implantable System for Remodulin®.

b. Patients with hearing loss may not be able to hear pump error alarms coming from the implanted pump, which may cause delay in therapy if the patient does not hear the alarm and contact the physician in a timely manner.

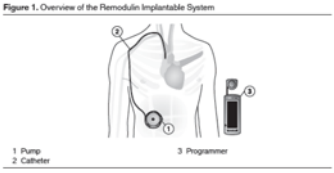
V. DEVICE DESCRIPTION

The Implantable System for Remodulin® consists of the following components:

- Medtronic SynchroMed II 8637P Programmable Pump (the "pump")
- Medtronic 8201 Implantable Intravascular Catheter (the "catheter")
- Medtronic N'Vision 8840 Clinician Programmer with 8870 Application Card (the "programmer")

Remodulin (treprostinil) Injection ("Remodulin") is stored in the pump reservoir and, per a programmed prescription, moves through the pump tubing, the catheter port, and the catheter to the intravascular delivery site. The programmer is a handheld device for healthcare provider use only that is used to review and program pump parameters using telemetry, a radio frequency (RF) communication (see Figure 1).

Figure 1. Overview of the Implantable System for Remodulin®

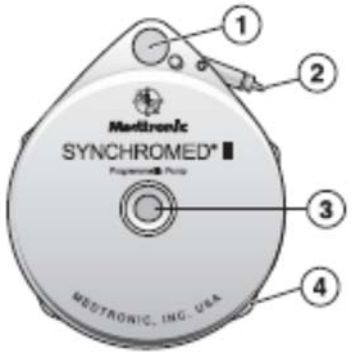


The pump reservoir may be refilled with Remodulin following a percutaneous procedure using the Medtronic Model 8551 Refill Kit.

Pump description

The 8637P implantable programmable pump is part of an infusion system that stores and delivers a prescribed drug to a specific site. The catheter connects to the pump catheter port. The pump is anchored in the pump pocket using the suture loops located on the outside of the pump (see Figure 2).

Figure 2. Pump exterior view



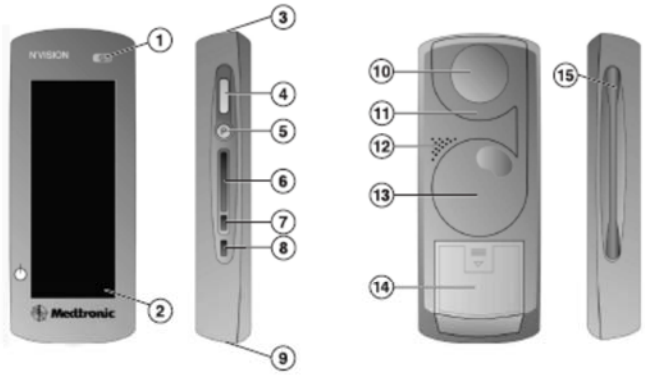
1 Catheter access port
2 Catheter port on the pump
3 Reservoir fill port
4 Suture loop

The drug is stored in the pump reservoir. Per a programmed prescription, the drug moves from the pump reservoir through the pump tubing, the catheter port, and the catheter to the infusion site. The catheter access port (CAP) can be used to assess catheter patency using a Model 8540PAH Catheter Patency Kit. The catheter access port allows entry of a 24-gauge noncoring needle to prevent accidental injection during refill procedures. The refill procedure uses a 22-gauge noncoring needle supplied in the refill kit.

Programmer description

The programmer (see Figure 3) with application card is a handheld device for programming Medtronic devices for drug therapies. Instructions specific to the 8870 software application for the Implantable System for Remodulin® are included in the Implantable System for Remodulin® Technical Manual.

Figure 3. Programmer components



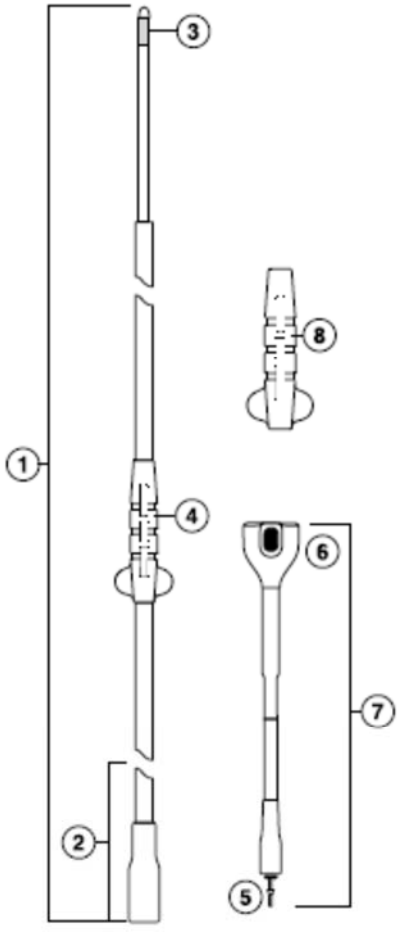
1 Therapy stop key
2 Touchscreen display
3 Infrared port
4 Scroll wheel
5 Programming key
6 Application card port
7 Application card ejection key
8 Power key
9 Expansion port
10 Magnet slot
11 Programming head
12 Speaker
13 Cable reel
14 Battery compartment
15 Touch pen storage

Catheter description

The 8201 catheter and the sutureless connector are part of the Medtronic Implantable System for Remodulin® that store and deliver Remodulin® (treprostinil) Injection into the bloodstream. Remodulin is released through a one-way valve (sleeve valve) located at the distal (cardiac) tip of the catheter (see Figure 4). The sleeve valve is designed to minimize blood ingression into the catheter lumen and precludes aspiration of blood from the catheter and the catheter access port.

The catheter is made of radiopaque silicone with enhanced radiopacity at the distal tip. The catheter is available in an 80 cm length.

Figure 4. Catheter with the sutureless connector



1 Catheter body
2 Catheter connector
3 Sleeve valve
4 Anchoring sleeve
5 Sutureless connector pin
6 Sutureless pump connector
7 Sutureless connector
8 Retention sleeve

Catheter accessories and descriptions

Anchoring sleeve – The anchoring sleeve secures the catheter to decrease the risk of migration. The anchoring sleeve is designed to decrease the risk of damage to the catheter body caused by tight sutures.

Sutureless connector – The sutureless connector is the proximal portion of the catheter, which joins the catheter to the pump at the catheter port. The connector pin joins the distal portion of the catheter to the sutureless connector, and the sutureless pump connector joins the sutureless connector to the pump.

Vein lifter – The vein lifter facilitates introducer insertion into a vein.

Retention sleeve – The retention sleeve is used when additional sutures are desired to secure the catheter.

The following components are compatible with the Implantable System for Remodulin®:

- Medtronic Model 8551 Refill Kit
- Medtronic Model 8540PAH Catheter Patency Kit
- Medtronic Model 8590 Mesh Pouch Accessory Kit (optional).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Remodulin is approved for chronic delivery via an external infusion pump either by subcutaneous infusion or by an indwelling central venous catheter for those patients who have failed subcutaneous infusion. Treatment for PAH typically occurs according to the ACC or ESC published guidelines at a center specializing in PAH and is primarily pharmacological progressing from oral to inhaled and eventually subcutaneous or intravenous infusion as the disease progresses. Lung transplantation may be appropriate for some patients.

VII. MARKETING HISTORY

The Implantable System for Remodulin® has not been market released in any country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Table 1 summarizes the potential adverse events related to the Implantable System for Remodulin®. The check marks indicate the components and procedures where the individual adverse events may occur. Refer to the Remodulin drug labeling for adverse events related to Remodulin.

Table 1: Potential Adverse Events for the Implantable System for Remodulin®

Adverse event	Pump	Catheter	Implant Procedure	Refill procedure
Air Embolism			X	
Allergic or immune system response	X	X	X	X
Anesthesia-related nausea and vomiting			X	
Back pain related to lying on the table			X	
Catheter dislocation		X	X	
Catheter occlusion		X		
Component failure resulting in loss of therapy or inability to program the pump	X	X		
Damage to components	X	X	X	X
Death	X	X	X	X
Disconnection or breakage	X	X	X	
Erosion	X	X	X	X
Fibrillation and other arrhythmias		X	X	
Hematoma	X	X	X	X
Hemorrhage and exsanguination			X	
Improper injection through the catheter access port			X	X
Infection or sepsis	X	X	X	X
Injection into pocket or subcutaneous tissue				X
Local or systemic Remodulin toxicity and related side effects	X	X	X	X
Low-grade fever			X	
Mild or moderate bruising or ecchymosis			X	X
Nerve damage			X	
Overfilling the reservoir			X	X
Pulmonary arterial hypertension symptoms—mild exacerbation			X	
Pain	X	X	X	X
Pneumothorax and hemothorax			X	
Pocket site and incisional pain	X		X	
Poor healing over the pump and catheter incisions	X	X	X	
Premature end of device service life	X			
Programming error	X		X	X
Pulmonary embolism or paradoxical embolism		X	X	
Pump inversion or migration	X		X	
Puncture of diaphragm, abdominal organs, or thoracic organs			X	
Remodulin overdose	X	X	X	X
Remodulin subcutaneous delivery	X	X	X	X
Remodulin underdose and abrupt cessation	X	X	X	X
Seroma	X	X	X	X
Shoulder pain, discomfort, or stiffness			X	
Sleep problems (insomnia)			X	
Stroke		X	X	
Underdose	X	X	X	X
Venous or asterial dissection of perforation			X	
Venous thrombosis, occlusion, stenosis, insufficiency or phlebitis		X	X	

IX. SUMMARY OF PRECLINICAL STUDIES

The Medtronic N'Vision Clinician Programmer and SynchroMed II programmable pump are commercially available. These devices were previously evaluated via non-clinical laboratory testing including: bench testing (including hardware/software verification and validation), biocompatibility testing, and animal studies. The test procedures and results were previously reviewed and approved in P860004. Remediation of the SynchroMed II was ongoing during the evaluation of the Implantable System for Remodulin®. FDA evaluated the design specification documents and remediation activities for SynchroMed II within the context of the Implantable System for Remodulin®.

SynchroMed II programmable pump for the Implantable System for Remodulin® drug compatibility studies, catheter design and system testing were conducted. Tests are summarized below.

A. Laboratory Testing

1. Toxicological, Biocompatibility and Biostability

There are two components of the Implantable System for Remodulin® with blood or tissue contact:

Model 8637 SynchroMed II programmable pump for the Implantable System for Remodulin® (CFN 8637P40). The pump is identical to the FDA approved Model 8637 SynchroMed II pump with regards device materials, sterilization and packaging materials and processes. Intended tissue contact is also the same. No additional biocompatibility or biostability testing was performed for the pump.

Model 8201 implantable intravascular catheter. Biocompatibility testing was performed on the final, finished Model 8201 catheter design including cytotoxicity and material mediated pyrogenicity. An evaluation of biocompatibility and biostability was performed on the catheter to demonstrate that the components of the catheter are biocompatible and biostable. The biological evaluation, including exhaustive extractions, toxicological assessments, and chemical characterizations demonstrated compliance of the materials with ISO 10993-1. All materials were found to be biologically stable and safe such that the device is expected to perform as intended after exposure to the in vivo environment for the intended duration of the device life.

2. In vitro Engineering Testing

a. Drug-Device Compatibility Studies

A comprehensive evaluation of drug/device compatibility of Remodulin with the Implantable System for Remodulin® (ISR) has been performed. The drug-in-implantable infusion system stability characterization study supports labeling of Remodulin in the ISR for up to 16 weeks per refill cycle. No impact of the delivery system on the stability (pH, content, and impurities) of drug products is observed. The drug-in-implantable infusion system leachables characterization study and corresponding toxicology assessments indicate that the exposure to chemicals leaching from the ISR system into the drug product are unlikely to cause toxic responses in patients implanted with the system. Drug impact on device has been evaluated as follows: drug-material compatibility testing, drug sorption correlation to mechanical integrity, and effect of drug on finished device after simulated in-use condition. Based on the results of these studies it is concluded that there is no impact on the elastomeric materials in the drug flow path or final finished device when in contact with the drug over the durations of the studies.

b. Pump Design Verification

Design verification testing of the Model 8637 SynchroMed II programmable pump for the Implantable System for Remodulin® (CFN 8637P40) was performed to verify the unique requirements to the ISR pump that are not already included in the FDA approved Model 8637 SynchroMed II programmable pump specification. All requirements were met.

c. Catheter Design Verification

Catheter design verification was performed on pre-conditioned, sterilized catheters to verify that product design output meets its design input requirements. Table 2 summarizes the purpose of each test and the results.

Table 2: Catheter Design Verification

Purpose of Testing	Results
Introducer Compatibility To verify the Model 8201 catheter can pass through an 8 Fr. introducer and be free of nicks, cuts, rips, and tears when visually inspected at 7X magnification.	Pass
Slitter Compatibility To verify the Model 8201 catheter is compatible for use with 8Fr slitters and be free of nicks, cuts, rips, and tears when visually inspected at 7X magnification.	Pass

Purpose of Testing	Results
Tunneling Tool Compatibility To verify the Model 8201 catheter can pass through a 13.8 Fr. tunneling tool and be free of nicks, cuts, rips, and tears when visually inspected at 7X magnification.	Pass
Insertion of Connector Pin To verify the force required for the first full insertion of the sutureless connector pin into the proximal portion of the catheter body is acceptable.	Pass
Separation of Connector To verify the junction strength between the catheter and sutureless connector pin after 5 connections and disconnections is acceptable.	Pass
Tip Stiffness To verify the stiffness force of the Model 8201 catheter's tip is acceptable.	Pass
Anchor Sleeve Repositionability To verify the anchoring sleeve is repositionable on Model 8201 catheter prior to fixation onto the catheter and the anchor sleeve does not slide freely when the catheter is held in a vertical position.	Pass
Initial bolus Flush To verify the Model 8201 catheter is not damaged from water injection into the connector of the catheter and the water only flows out of the proximal edge of the sleeve valve. Visual inspection at 7X magnification to confirm no nicks, cuts, rips and tears.	Pass
Sleeve Valve Flow To verify the Model 8201 catheter's operating pressure for steady state fluid flow is acceptable.	Pass
Anchor Sleeve Fluid Flow To verify the Model 8201 catheter's operating pressure for steady state fluid flow with the anchor sleeve secured onto the catheter body is acceptable.	Pass
U-Bend Flow To verify the Model 8201 catheter's operating pressure for steady state fluid flow with the coil reinforced portion of the catheter body held in a tight curvature is acceptable.	Pass
Flow with Compressive Load from the Pump To verify the Model 8201 catheter's operating pressure for steady state fluid flow with the coil reinforced portion of the catheter body overlapped once and a compression force applied is acceptable.	Pass
Fluid Leakage	Pass

Purpose of Testing	Results
To verify an occluded Model 8201 catheter can withstand required pressure without leaking.	
Sleeve Valve Function To verify the Model 8201 catheter's sleeve valve prevents fluid ingression into the catheter lumen. The sleeve valve is inspected for nicks, cuts, rips, and tears at 7X magnification.	Pass
Distal Tip Attachment Strength To verify the Model 8201 catheter's tip attachment strength to the inner tubing is acceptable.	Pass
Composite Tensile Strength To verify the Model 8201 catheter's tensile strength between the distal end and the connector is acceptable.	Pass
Anchor Sleeve Retention Strength To verify the Model 8201 anchor sleeve's grip strength on the catheter body is acceptable.	Pass
Radiopacity Continuity and Tip Radiopacity To verify the Model 8201 catheter is continuously radiopaque from tip to pump-end of the sutureless connector and the Model 8201 catheter's tip is more radiopaque than the distal portion.	Pass
Catheter Body Flex Life To verify the Model 8201 catheter's coil reinforced flex strength at a defined flex cycle and bend radius is acceptable.	Pass
Catheter Body Crush Resistance To verify the hoop strength of the coil reinforced section of the Model 8201 catheter is acceptable.	Pass
MRI Catheter Body Heating To verify the Model 8201 catheter's heating in a 1.5T and 3T MRI environment is acceptable.	Pass
MRI Induced Catheter Body Force and Torque To verify the induced force and torque of the Model 8201 catheter in a 1.5T and 3.0T MRI environment is acceptable.	Pass
Environmental Conditions To verify the environmental conditions associated with shipping, (Temperature, vibration, impact forces) do not affect the functional characteristics of the Model 8201 catheter.	Pass

Purpose of Testing	Results
Drug Permeability To verify the rate of Trepostinil sodium permeation through the inner tubing of the Model 8201 catheter is acceptable.	Pass

d. Sterilization, Packaging and Shelf-life

The Model 8637 SynchroMed II programmable pump for ISR (CFN 8637P40) is identical to the FDA approved Model 8637 SynchroMed II pump (P860004) with regards materials, manufacturing processes, sterilization and packaging. No additional sterilization, packaging and shelf-life testing was performed for the pump.

- Sterilization: For the Model 8201 implantable intravascular catheter sterilization testing demonstrates a Sterility Assurance Level (SAL) in excess of 10^{-6} is achieved when the Model 8201 implantable intravascular catheter product family is sterilized in a defined load configuration.
- Packaging: For the Model 8201 implantable intravascular catheter sterilization packaging testing packaging testing was performed in accordance to ASTM D4169, distribution cycle 13, assurance level I (most stressful) to simulate air and motor freight shipping distribution cycle. Sterile barrier systems were tested for package integrity after exposure to sterilization, environmental conditioning. All tests met acceptance criteria. Sterile package integrity was maintained.
- Shelf-life: The Model 8201 Catheter will be labeled with a use-by-date of twenty-four (24) months from date of assembly of the sterilized package. Testing was completed and supports the 24 month shelf-life for both packaging and catheter performance.

e. Software

In accordance with FDA's Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (May 11, 2005), the PMA included the FDA recommended software documentation to be provided in submissions for medical device software with a 'Major' level of concern. Analysis and testing was performed and demonstrates that the ISR software operates per specification

f. Human Factors Validation Testing

Human factors validation testing was completed for the ISR and included 2 individual studies: programmer user interface and programmer labeling; and Patency kit. The studies demonstrated use errors. In order to mitigate these risks, Medtronic has agreed, as a condition of approval, to validate a training program and the device is restricted with respect to training, per section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act.

g. System Testing

In addition to the clinical study, the system validation effort included bench testing on production units to validate that the system conformed to the project-defined user

needs and intended uses under simulated use conditions. All User needs and Intended Uses have been successfully validated with passing results.

B. Animal and Cadaver Studies

Medtronic has conducted one **chronic GLP study** to evaluate the safety/effectiveness of the implantable intravascular catheter and pump system. Chronic system performance of the implantable intravascular catheter was demonstrated with both the low rate infusion of saline and Remodulin Injection. Pump refill volumes and pressure waveform data support that the catheter was patent throughout the study. The radiographs of the implanted system showed no evidence of dislocation, kinking, or discontinuity thereby demonstrating stability and integrity of the implanted system. Data from this study demonstrated there are no significant adverse effects as a result of the use of the implantable system in animals.

A human cadaver non-GLP study was conducted to validate the software and labeling used in describing operational steps for the implantation and programming of the Implantable System for Remodulin®. Typical use scenarios during implant, follow-up, and system revisions were performed using a perfused human cadaver model. The tested sections of the Implantable System for Remodulin®'s software and manuals and patency kit successfully met the study objectives: the software functioned as described in the manual, and the procedures steps in the labeling are complete and accurate.

X. SUMMARY OF PRIMARY CLINICAL STUDY

Table 3: Summary of Primary Clinical Study

Clinical Study	Study Design	Objective	Number of Sites	Number of Subjects Enrolled
Pivotal	Multi-center, prospective, clinical trial	Evaluate the safety of the intravascular catheter	10	64

The DelIVery for Pulmonary Arterial Hypertension (PAH) Clinical Study demonstrated the Implantable Intravascular Catheter is reasonably safe when used with the Medtronic SynchroMed II Implantable Infusion System to deliver Remodulin. The DelIvery for PAH clinical study provides safety information on the Model 10642 Implantable Intravascular Catheter, which is applicable to and supports safety of the Model 8201 Implantable Intravascular Catheter and Implantable System for Remodulin®.

A. Study Design

The purpose of the clinical trial is to evaluate the safety profile of the Model 10642 Implantable Intravascular Catheter, a component of the PAH Implantable Vasodilator Therapy (PIVoT) system. The PIVoT system includes the SynchroMed® II Implantable Infusion System (Model 8637), the Implantable Intravascular Catheter (with sutureless connector) (investigational, Model 10642), and the N'Vision Clinician Programmer (Model 8840) with application software

card (Model 8870). This system is used to deliver Remodulin® (treprostinil) Injection, a currently marketed pharmaceutical. This report provides safety information on the Model 10642 Implantable Intravascular Catheter, which is applicable to and supports market release of the Model 8201 Implantable Intravascular Catheter and Implantable System for Remodulin®.

The clinical study is designed as a multi-center, prospective, single arm, non-randomized open label Investigational Device Exemption (IDE) clinical study. Up to 70 subjects at 10 centers were planned for implant and follow-up. This study is conducted in the United States. The study enrolled subjects who met the approved Remodulin indication, using the approved concentrations, and approved intravenous route of administration and who met all inclusion and no exclusion criteria.

Implanted subjects were seen at scheduled follow-up visits; one week, six weeks, three months, six months, twelve months, and then every six months thereafter. The primary endpoint was evaluated once all active subjects completed the six month follow-up visit, and a minimum of 22,000 patient days among implanted subjects were accumulated.

1. Subject Inclusion and Exclusion Criteria

Patients who met all inclusion and no exclusion criteria were eligible.

Inclusion Criteria

- Patient is 18 years of age or older
- Patient (or patient's legally authorized representative) is willing and able to provide written informed consent
- Patient is willing and able to comply with the protocol, including required follow-up visits
- Patient is diagnosed with Pulmonary Arterial Hypertension (World Health Organization (WHO) Category Group 1 [by the WHO Clinical classification system]), including:
  - Idiopathic (IPAH)
  - Heritable PAH (HPAH)
  - Associated with PAH (APAH), with exceptions as noted in exclusion criteria below
- Patient is receiving continuous infusion of Remodulin therapy via intravenous delivery using an external drug delivery pump system. Patient has been at a stable Remodulin dose (no change in dose) for at least four weeks
- Patient’s anticoagulation therapy can be managed to permit safe device implantation
- Patient has no history of pulmonary embolism since the initiation of subcutaneous or IV therapy for PAH

Exclusion Criteria

- Patient is a woman who is pregnant, nursing, or of child bearing potential and is not on a reliable form of birth control
- Patient is enrolled, has participated within the last 30 days, or is planning to participate in a concurrent drug and/or device study during the course of this clinical

trial. Co-enrollment in concurrent trials is only allowed with documented pre-approval from the Medtronic study manager that there is not a concern that co-enrollment could confound the results of this trial

- Patient has been initiated on a new oral PAH therapy in the last two months
- Patient has had a recent (within three months) or otherwise unresolved infection requiring antibiotic treatment
- Patient is diagnosed with PAH associated with hemoglobinopathies (sickle cell anemia, thalassemia), HIV, schistosomiasis, portal hypertension, pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis
- Patient is implanted with electrical stimulation medical devices(s) anywhere in the body (e.g., cardiac pacemakers, implantable cardioverter defibrillators (ICDs), spinal cord stimulators). This includes implanted leads and electrodes or abandoned leads and electrodes from an explanted device
- Patient is diagnosed with chronic kidney disease (serum creatinine > 2.5 mg/dl) within 90 days prior to baseline visit; chronic kidney disease is defined as that lasting or expected to last more than 3 months
- Patient is a person for whom the implantable vascular catheter length of 80 cm was excessively long or too short to be properly implanted
- Patient has an existing external catheter(s) that would remain in place after the pump implant
- Patient is a person for whom the implantable pump cannot be implanted 2.5cm or less from the skin surface
- Patient is a person whose body size is not sufficient to accept implantable pump bulk and weight
- Patient is at increased susceptibility to systemic or soft tissue infections as determined by physician
- Patient is Functional Class IV (New York Heart Association (NYHA))

2. Follow-up Schedule

Implanted subjects were seen at scheduled follow-up visits; one week, six weeks, three months, six months, twelve months, and then every six months thereafter.

3. Clinical Endpoints

There was one primary endpoint. The objective was to demonstrate that the Model 10642 Implantable Intravascular Catheter is safe when used with the Medtronic SynchroMed II Implantable Infusion System to deliver Remodulin.

The results of the primary safety analysis, summarized in Table 4, demonstrate that the primary safety objective was met, demonstrating that the Model 10642, when used with the Medtronic SynchroMed II Implantable Infusion System to deliver Remodulin, is safe. This was shown by the low a favorable comparison of the rate of catheter- related complications compared to an objective performance criteria derived from literature.

Published data in the PAH population suggests a rate of central venous catheter (CVC) systemic infections for bloodstream infections (BSI) at 0.43 to 1.13 per 1000 patient days

and site infections at 0.26 to 0.87 per 1000 patient days while complications from catheter thrombosis, mechanical dysfunction, and catheter dislocation in the general CVC population contribute another 0.36, -0.51 events per 1000 patient days. This was used to calculate a combined rate of catheter-related complications of up to 2.5 per 1000 patient days.

Table 4: Summary of Primary Safety and Effectiveness Results

Data as of	Performance Goal	Patient Days	Catheter-related Complications	Catheter-related Complications Per 1000 Days	One-sided upper 97.5% confidence bound	P-value
June 21, 2013	Rate per 1000 days < 2.5	22,013	6	0.27	0.59	<0.0001
January 11, 2017		89,935	7	0.08	0.16	<0.0001

Ancillary Objectives

The study further characterized the system effectiveness and symptom relief, quality of life, and ease of use, healthcare utilization assessments, and subject/caregiver involvement in system management of the system through the ancillary objectives. These objectives are descriptive in nature and there were not powered hypotheses to be tested. Table 5 presents a summary of the ancillary objectives.

As expected, effectiveness variables including Quality of Life (QoL) (CAMPHOR and EQ-5D questionnaires), 6-Minute Walk, New York Heart Association Functional Classification showed little or no change when comparing the external pump (baseline) to the implanted pump; this was expected since the treatment therapy (Remodulin) is the same. In addition, similar results were observed within a third QoL assessment, the FACIT-TS-G questionnaire. 100% of subjects rated their overall satisfaction with the implantable system as good, very good or excellent at both 6 and 26 weeks.

Table 5: Summary of Ancillary Objectives Results

Objective	Results
To characterize percent change of six-minute walk test distance from baseline to 6 weeks post-implant	Mean percent increase in six-minute walk from baseline to 6 weeks post-implant: 0.2% ± 19.3% 95% confidence interval: -4.9 – 5.2%
To characterize changes in quality of life	CAMPHOR (QoL Scale) change from baseline to 6 months EQ-5D Mean absolute change at 6 months ± S.D.: -0.01 ± 0.10 95% confidence interval: -0.04 – 0.02
To characterize the incidence of adverse events	Subject experience included 64 enrolled subjects, and 246 years of implanted follow-up time in 60 subjects. During that time, there were 1222 Adverse Events: 325 adverse events related to procedure, drug pump, catheter, programmer, Remodulin Injection, refill process, catheter patency test, implant tools, or Model 8540 Catheter Access Port Kit 897 adverse events not related to the items listed above
To characterize healthcare utilization (hospitalizations, emergency room visits, and urgent clinic visits)	At 12 months post-implant: • 45.6% had been hospitalized. • 53.3% had been in the ER or hospitalized. • 56.7% had been to urgent care, been to the ER, or were hospitalized.

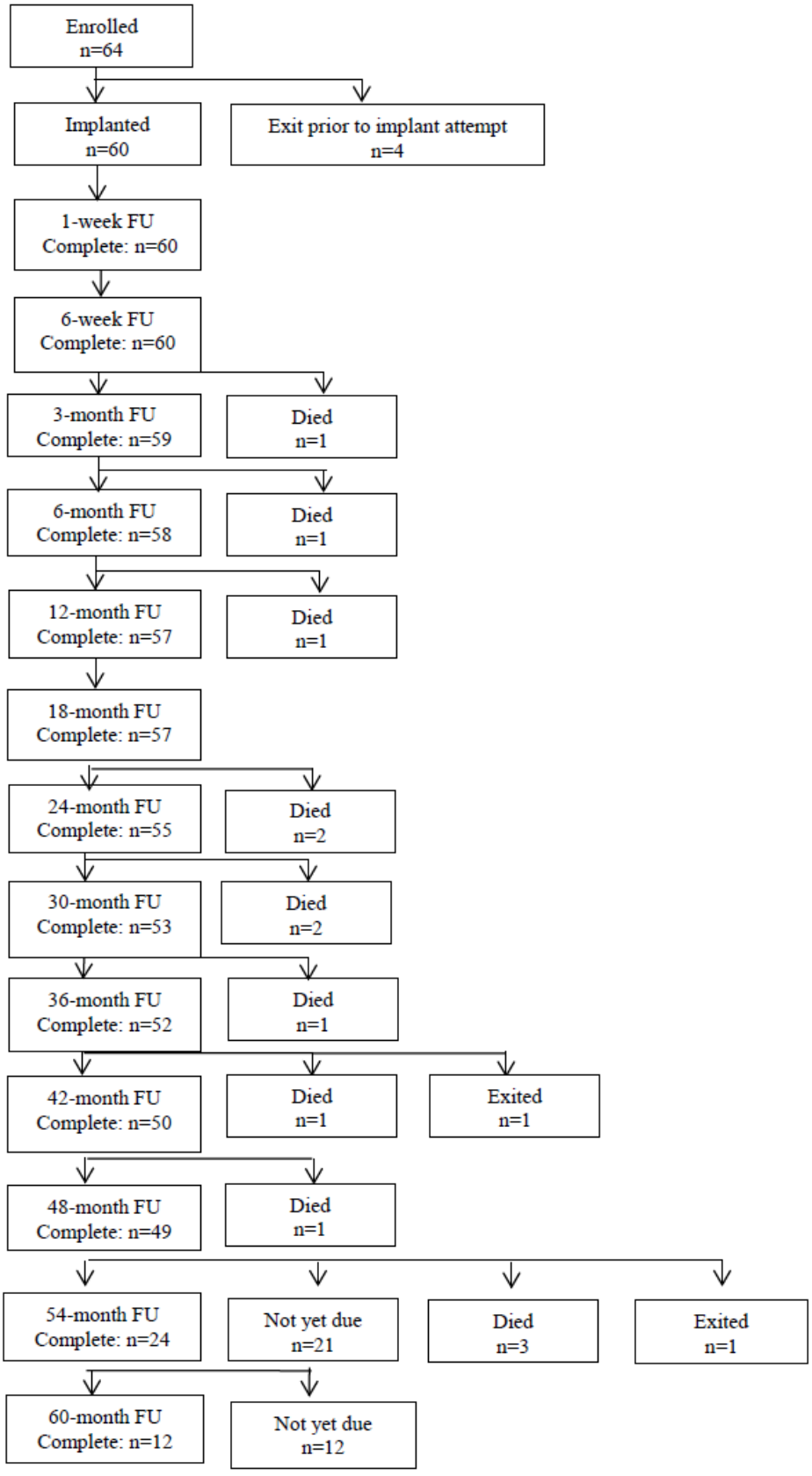
B. Accountability of PMA Cohort

The first subject was enrolled on June 14, 2011, and the final subject was enrolled on November 20, 2012. A total of 64 subjects were enrolled in the DelIVery for PAH clinical study at ten investigational sites in the United States. Of the 64 subjects, there were 60 attempted implants and all 60 were successfully implanted with the system.

It was pre-specified in the study protocol that the primary objective of the study would be analyzed when 22,000 patient days of follow-up had occurred and all active subjects completed the six month follow-up visit. The primary endpoint data in this report were reported per protocol and includes any visit or event that occurred on or before June 21, 2013. All other data in this report is from data collected on case report forms on or before January 11, 2017 and received at Medtronic on or before March 3, 2017 unless otherwise specified/noted.

Of the 60 implanted subjects, there were 89,935 days of follow-up (range 87-1996 days per subject). Study subject disposition is displayed in Figure 5.

Figure 5. Enrolled Subject Status Flow Chart



C. Study Population Demographics and Baseline Parameters

1. Subject Demographics

Table 6 presents baseline information for all 64 subjects enrolled, including the four subjects who exited prior to implant, and the 60 subjects who were implanted.

Table 6: Baseline Demographics

Subject Characteristics	Non-implanted Subjects (n = 4)	Implanted Subjects (n = 60)	Total Subjects (n = 64)
Gender (N, %)			
Male	1 (25%)	12 (20%)	13 (20%)
Female	3 (75%)	48 (80%)	51 (80%)
Age (years)			
Mean ± Standard Deviation	49.8 ± 16.9	50.1 ± 13.5	50.1 ± 13.5
Median	52.5	52.0	52.0
25^{th} Percentile - 75^{th} Percentile	36 - 64	38 - 61	38 - 61
Minimum – Maximum	29 - 65	24 - 74	24 - 74
Race / Ethnic Origin (N, %)			
Subject/physician chose not to provide information	0 (0%)	0 (0%)	0 (0%)
Not reportable per local laws or regulations	0 (0%)	0 (0%)	0 (0%)
American Indian or Alaska Native	0 (0%)	0 (0%)	0 (0%)
Asian	0 (0%)	2 (3%)	2 (3%)
Black or African American	0 (0%)	3 (5%)	3 (5%)
Hispanic or Latino	1 (25%)	8 (13%)	9 (14%)
Native Hawaiian or Pacific Islander	0 (0%)	0 (0%)	0 (0%)
White or Caucasian	3 (75%)	47 (78%)	50 (78%)
Two or more races	0 (0%)	0 (0%)	0 (0%)
Other race	0 (0%)	0 (0%)	0 (0%)

D. Safety and Effectiveness Results

1. Safety Results

All adverse events (AEs) were reported throughout the study, starting at subject enrollment. Documented pre-existing conditions were not considered AEs unless the nature or severity of the condition had worsened.

Adverse Events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) which used a five step hierarchical system, starting with the Lowest Level Term (LLT) (level 1) or diagnosis and progressively losing specificity up to a System Organ Class (SOC) (level 5). Preferred Terms (PT) are used in the summary tables except catheter dislodgement which is a LLT.

Anticipated adverse events were collected in the study. Table 7 lists the events and the time frame for which they were considered anticipated. An event was considered anticipated if the onset and resolution occurred within the specified timeframe.

Table 7: Anticipated AEs Related to Implant Procedure

Event Description	Time Frame (Hours) from the Surgical Procedure
Anesthesia-related nausea/vomiting	24
Low-grade fever (<100°F or < 37.8°C)	48
Pocket site / incisional pain	72
Mild to moderate bruising / ecchymosis	168
Sleep problems (insomnia)	72
Back pain related to lying on the table	72
Shoulder pain/discomfort/stiffness related to shoulder immobilization during procedure	72
Mild exacerbation of PAH symptoms	24

All AEs and deaths were reviewed by an independent Adverse Events Adjudication Committee (AEAC). The AEAC adjudicated each event for event MedDRA code, seriousness, relatedness and when applicable, complication/observation. The definition of a complication is used for determination of the events counted towards the primary objective analysis. A complication is defined as an adverse event that results in death, involves any termination of significant device function, or requires an invasive intervention.

Table 8: Adverse Event Definitions

General	
Adverse Event (AE)	Any untoward medical occurrence in a subject NOTE: This definition does not imply that there is a relationship between the adverse event and the device under investigation. (ISO14155-1:2003(E) 3.2)
Seriousness	

Serious Adverse Event (SAE)	Serious Adverse Events include adverse events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, and are life-threatening, a persistent or significant disability/incapacity or a congenital anomaly/birth defect. Other important medical events, based upon appropriate medical judgment, may also be considered Serious Adverse Events if a trial participants' health is at risk and intervention is required to prevent an outcome mentioned. (FDAAA, U.S. Public Law 110-85, Title VIII Section 801)

Results

There were 1222 adverse events reported for 62 out of the 64 enrolled subjects. Of these 1219 involved the 60 subjects who were implanted with the PIVoT system. Three AEs occurred in 2 of the 4 subjects who never attempted implant. Of the 1222 adverse events, 1214 (99.3%) have been fully adjudicated by the AEAC. The timing of the event onset (i.e. pre, during and post-implant) was assessed by the site principal investigator and was not adjudicated by the AEAC. Table 9 is a high-level summary of all adverse events collected in the study.

Table 9: Adverse Event Summary

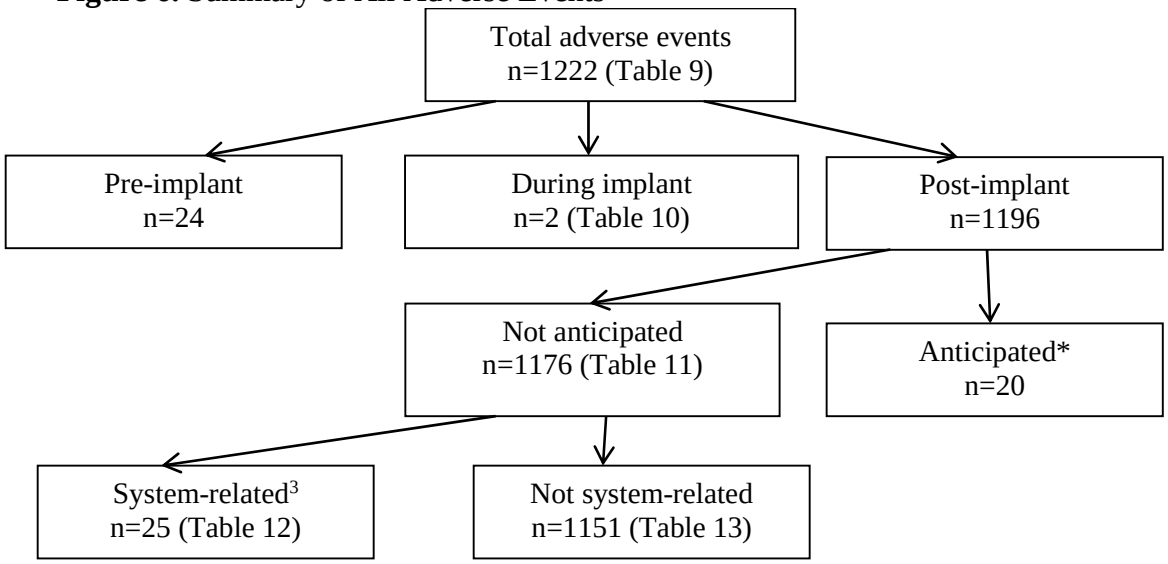
AE Timing	Related[1]	Not Related	Total Adverse Events
Pre-implant	1	23	24
During implant[2]	2	0	2
Post-implant	322	874	1196
Total	325	897	1222

There are a number of summary tables in this section. Figure 6 shows how the AE data are categorized in the following tables (Table 9 through Table 13).

[1] Related to procedure, drug pump, catheter, programmer, Remodulin Injection, refill process, catheter patency test, implant tools, or Model 8540 Catheter Access Port Kit

[2] After skin incision and prior to completion of skin closure

Figure 6. Summary of All Adverse Events



*Anticipated events are listed in Table 7.

There were 24 pre-implant AE's in the study. One (infusion site pain) was related to the system/procedure and adjudicated as Implant Procedure and Remodulin related, as this was due to the temporary external peripheral Remodulin infusion line placed at least one day prior to implant (part of the implant procedure). Three of the pre-implant AE's were device related infection from the subject's pre-existing PICC line, two AE's were reported for hypokalemia, two for vessel site puncture pain, and all other AE's were single events.

Two adverse events with onset assessed by the site as occurring during implant are summarized in Table 10.

[3] System-related means related to the catheter, pump, or programmer.

Table 10 Adverse Events Occurring During Implant

Preferred Term	Description (Verbatim from CRF)	Actions Taken	Relatedness
Atrial fibrillation	Patient has history of atrial flutter. Per anesthesia note "beginning of procedure, NSR, began intermit atrial fib/flut during access to vein. Continuous Afib with catheter placement." "I spoke directly to Dr. (redacted name of anesthesiologist) this afternoon and he stated the patient was in normal sinus rhythm at the beginning of the case with "intermittent atrial arrhythmias".	Other diagnostic tests / procedures (Noted during cardiac monitoring during the implant procedure.), Medications administered, Other actions taken (cardioversion; resolved the atrial fibrillation)	Implant Procedure
Pneumothorax	Subject transferred to PACU from OR. Subject was noted to be dyspneic, oxygen saturations 80's and hypotensive, SBP 80s and severe pain. CXR obtained and modest right pneumothorax was seen. The AE is related to placement of implantable catheter. Subject treated with supplemental oxygen (100% non-rebreather mask), fluid bolus administered and Dilaudid IV given for pain. Subject hemodynamically stable and transferred to patient care unit.	Chest X-ray, Other diagnostic tests / procedures (1/10/12 chest x-ray post-op - moderate right pneumothorax), Prolongation of existing hospitalization, Medications administered, Other actions taken (100% Non-rebreather Oxygen Mask)	Implant Procedure, Implant tool(s)

Following the 60 implants and excluding anticipated adverse events, there were 1176 post-implant adverse events, which are summarized in Table 11.

Table 11: Post-Implant Adverse Event Summary Excluding Anticipated

Adverse Event Classification	Number of Events (Number of Subjects, % of Subjects) (n=60)
Serious	
Yes	190 (46, 76.67%)
No	985 (60, 100.00%)
Unknown	1 (1, 1.67%)
Unanticipated[4]	0(0,0.0%)

[4] Four pump events occurred at the time of this report, (1 high resistant battery ERI, 3 pump motor stalls). The individual events are not considered unanticipated. Medtronic investigated these events collectively as a UADE because of the rate of reported stopped pumps. **The current estimated survival probability at 60 months (82.5%) is below the projected survival rate (85.9%).**

Adverse Event Classification	Number of Events (Number of Subjects, % of Subjects) (n=60)
Procedure Relatedness	
Related	149 (54, 90.00%)
Implant Procedure	137 (54, 90.00%)
System Modification	12 (5, 8.33%)
Not related	1027 (60, 100.00%)
Unknown	0(0,0.0%)
System Relatedness	
Related	25 (19, 31.67%)
Model 10642 Catheter	6 (3, 5.00%)
SynchroMed II Pump	19 (16, 26.67%)
Not related	1151 (60, 100.00%)
Unknown	0(0,0.0%)
Remodulin Injection	
Related	139 (40, 66.67%)
Not related	1031 (60, 100.00%)
Unknown[5]	6 (4, 6.67%)
Refill Process	
Related	95 (38, 63.33%)
Not related	1080 (60, 100.00%)
Unknown	1 (1, 1.67%)
Implant Tool	
Related	1 (1, 1.67%)
Not related	1175 (60, 100.00%)
Unknown	0(0,0.0%)
Model 8540 Catheter Access Port Kit	
Related	0(0,0.0%)
Not related	1176 (60, 100.00%)
Unknown	0(0,0.0%)

[5] Green loose stool and abdominal cramping were reported for the same subject 16 days post implant. The site PI and AEAC could not rule out that these symptoms may be related to Remodulin.

Adverse Event Classification	Number of Events (Number of Subjects, % of Subjects) (n=60)
Catheter Patency test	
Related	0(0,0.0%)
Not related	1176 (60, 100.00%)
Unknown	0(0,0.0%)
Total	**1176 (60, 100.00%)**

Note: An event may be both procedure-related and system-related
Note: An event may be related to more than one procedure or component.

A system-related adverse event is defined as an adverse event related to one or more of the system components: the catheter, pump, and programmer. Excluding anticipated adverse events, there were 25 system-related (pump or catheter) adverse events occurring in the study. There were no events deemed related to the programmer. They are summarized in Table 12.

Table 12: Post-Implant System-related Adverse Events

Adverse Event Preferred Term	Number of Events (Number of Subjects, % of Subjects) (n = 60)
Abdominal pain lower	1 (1, 1.67%)
Abdominal pain upper	1 (1, 1.67%)
Contusion	1 (1, 1.67%)
Dermatitis contact	1 (1, 1.67%)
Device battery issue	1 (1, 1.67%)
Device damage	2 (1, 1.67%)
Device dislocation	1 (1, 1.67%)
Device malfunction	3 (3, 5.00%)
Erythema	1 (1, 1.67%)
Implant site extravasation	3 (3, 5.00%)
Lead dislodgement	3 (2, 3.33%)
Medical device pain	3 (3, 5.00%)
Muscle spasms	1 (1, 1.67%)
Pulmonary arterial hypertension	1 (1, 1.67%)
Skin striae	1 (1, 1.67%)
Venous stenosis	1 (1, 1.67%)
Total	**25 (19, 31.67%)**

Among the 60 subjects and excluding anticipated adverse events, there were 1151 adverse events that were not related to the system (catheter, pump, or programmer), but some

adverse events may have been procedure-related. Non-system related adverse events that occurred 5 or more times are listed in Table 13, but some adverse events may have been procedure-related.

Table 13: Post-Implant Adverse Events Not Related to the System with 5 or More Occurrences

Preferred Term	Number of Events (Number of Subjects, %) (n=60)
Upper respiratory tract infection	61 (32, 53.33%)
Implant site pain	45 (43, 71.67%)
Pulmonary arterial hypertension	39 (21, 35.00%)
Dyspnoea	28 (20, 33.33%)
Headache	24 (18, 30.00%)
Injection site reaction	24 (16, 26.67%)
Nasopharyngitis	21 (15, 25.00%)
Immediate post-injection reaction	20 (16, 26.67%)
Fluid overload	18 (8, 13.33%)
Hypotension	18 (15, 25.00%)
Atrial fibrillation	17 (5, 8.33%)
Injection site pain	17 (13, 21.67%)
Pneumonia	17 (13, 21.67%)
Dizziness	16 (14, 23.33%)
Fatigue	15 (14, 23.33%)
Sinusitis	15 (11, 18.33%)
Nausea	14 (13, 21.67%)
Urinary tract infection	14 (9, 15.00%)
Bronchitis	13 (12, 20.00%)
Diarrhoea	13 (11, 18.33%)
Pain in extremity	13 (13, 21.67%)
Hypokalaemia	11 (7, 11.67%)
Implant site bruising	11 (10, 16.67%)
Abdominal pain	9 (9, 15.00%)
Anxiety	9 (8, 13.33%)
Dyspnoea exertional	9 (7, 11.67%)
Flushing	9 (9, 15.00%)
Influenza	9 (8, 13.33%)
Oedema peripheral	9 (7, 11.67%)

Preferred Term	Number of Events (Number of Subjects, %) (n=60)
Palpitations	9 (6, 10.00%)
Vomiting	9 (9, 15.00%)
Back pain	8 (8, 13.33%)
Rash	8 (6, 10.00%)
Right ventricular failure	8 (7, 11.67%)
Syncope	8 (7, 11.67%)
Musculoskeletal pain	7 (6, 10.00%)
Nasal congestion	7 (5, 8.33%)
Arthralgia	6 (5, 8.33%)
Depression	6 (6, 10.00%)
Gastrointestinal haemorrhage	6 (4, 6.67%)
Haemoptysis	6 (1, 1.67%)
Insomnia	6 (6, 10.00%)
Adverse drug reaction	5 (5, 8.33%)
Atrial tachycardia	5 (3, 5.00%)
Cardiac failure	5 (4, 6.67%)
Chest discomfort	5 (5, 8.33%)
Cough	5 (4, 6.67%)
Ear infection	5 (5, 8.33%)
Fluid retention	5 (4, 6.67%)
Gastrooesophageal reflux disease	5 (5, 8.33%)
Hypoxia	5 (4, 6.67%)
Musculoskeletal chest pain	5 (3, 5.00%)
Neck pain	5 (5, 8.33%)
Supraventricular tachycardia	5 (3, 5.00%)

Refill Reactions

Refill reaction is defined as reported adverse events (AEs) that were adjudicated by the AEAC as refill related, drug related, and not catheter related. A refill reaction is caused by subcutaneous leaking of Remodulin from the needle during withdrawal of needle from the reservoir septum at the end of the refill process. The refill reaction can be local, systemic, or systemic and local.

- Local: pain, erythema (redness), and/or swelling near pump/injection site
- Systemic: flushing, headache, nausea and/or hemodynamic changes
- Serious (clinical study/FDA definition) – hospitalization or life threatening event

In the clinical trial, it was demonstrated that chilling drug prior to the refill reduced the incidence and severity of the refill reactions. Refilling the pump with cold drug condenses the propellant surrounding the expandable/collapsible pump reservoir causing negative pressure for short duration in the pump reservoir. The negative pressure in the reservoir and refill needle causes drug in the needle to be pulled into the needle/extension tubing during withdrawal of the needle from the reservoir minimizing or eliminating subcutaneous delivery of a droplet of Remodulin. Table 14 summarizes the refill reactions.

Table 14: Summary of Refill Reactions

Refill Reaction	**Non-Chilled Drug Refills (n=1053)**	**Chilled Drug Refills (n=1176)**
Local N (%)	21 (2.0%)	9 (0.8%)
Systemic N (%)	8 (0.8%)	5 (0.4%)
Systemic and Local N (%)	13 (1.2%)	2 (0.2%)
Total Refill Reactions N (%)	**42 (4.0%)**	**16 (1.4%)**
Serious n (%)	10 (0.9%)	2 (0.2%)

Death Summary

There have been fourteen deaths as of July 12, 2017. These deaths were reviewed by the Adverse Event Advisory Committee (AEAC), and 13 were adjudicated as not related to the investigational system. One death was adjudicated as related to a pump failure. Table 15 summarizes the fourteen subject deaths.

Table 15: Summary of Subject Deaths

Subject	Days After First Implant	Cause of Death (Preferred Term)
M100800002	87	Cardiac failure
M100100002	129	Pulmonary embolism
M100100011	299	Right ventricular failure
M100500004	615	Cardiac failure
M100800004	728	Cardiopulmonary failure
M101000005	857	Cardiac arrest
M100600005	888	Respiratory failure
M100100012	995	Haemoptysis
M100800006	1139	Pulmonary arterial hypertension
M101000004	1420	PAH Disease Progression
M100100007	1472	Embolic strokes
M100500007	1525	Hemorrhagic shock
M100900002	1539	Acute on chronic systolic right heart failure
M101000002	1745	Pump failure

Discontinuation of Therapy

Three clinical study subjects had bilateral lung transplants. In all three cases prior to the lung transplant, the Remodulin delivery was transitioned to an external delivery system in anticipation of the lung transplant procedure. For the transition to an external delivery system the pump was filled with saline, transitioned by up titration of Remodulin with the external system. When all the Remodulin was out of the implanted system the implanted pump was programed to minimal rate. At the time the subjects received a bilateral lung transplant, two of the 3 implantable systems were fully explanted.

System Reliability

Data in this section is through July 12, 2017.

1. Catheter reliability

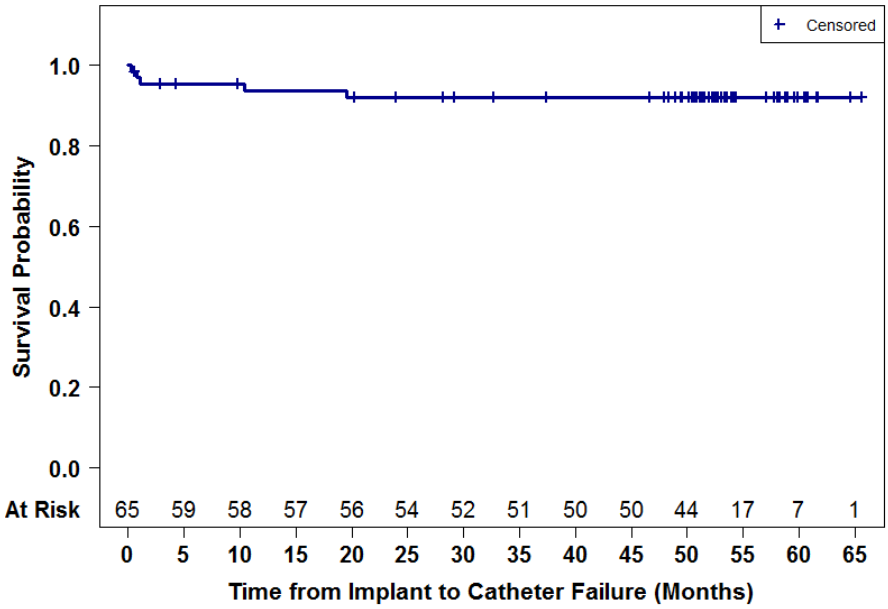
Catheter failures include adverse events that required replacement of the catheter. There were five events including: three catheter dislodgements from the vasculature (key term as lead dislodgement) and two subcutaneous leakage of Remodulin due to catheter puncture by needle during refill (key term as injection site reaction). Table 16 summarizes the catheter time from implant survival estimates. Figure 7 is a Kaplan-Meier curve of the data in Table 16.

Table 16: Survival estimates for the event Catheter Failure

Time from Implant to Catheter Failure (Months)	Survival Estimate	Survival Estimate 95% Confidence Limits
1	96.9%	(88.2%, 99.2%)

5	95.3%	(86.2%, 98.5%)
10	95.3%	(86.2%, 98.5%)
15	93.7%	(84.0%, 97.6%)
20	92.0%	(81.9%, 96.6%)

Figure 7. Kaplan-Meier Curve for event Catheter Failure



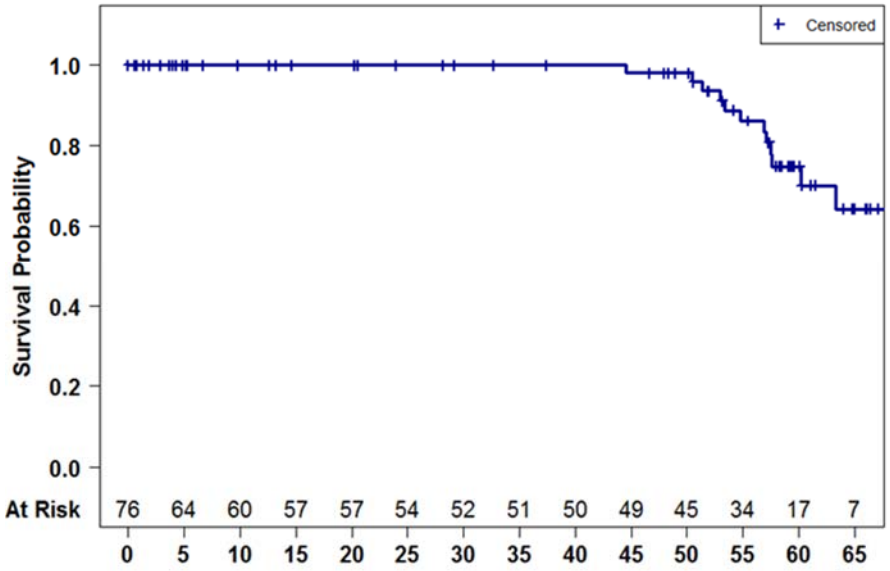
2. Pump reliability

There were thirteen pump replacement events due to all pump causes (pump reaching/nearing elective replacement indicator (ERI), pump failures, or other pump-related reason). Six pumps were replaced for expected ERI, five pumps replaced due to pump motor failure, one pump replaced due to premature ERI, and one replaced for low refill accuracy ratio. ERI will be triggered at 81 months post implant, but will be triggered earlier when the average flow rate is greater than 0.9 mL/day. Table 17 summarizes the pump time from implant survival estimates. Figure 8 is a Kaplan-Meier curve of the data in Table 17.

Table 17: Survival estimates for the event Pump Replacement due to Pump Cause

Time from Implant to Pump Replacement due to Pump Cause (Months)	Survival Estimate	Survival Estimate 95% Confidence Limits
40	100%	--
45	98.0%	(86.6%, 99.7%)
50	98.0%	(86.6%, 99.7%)
55	86.1%	(71.5%, 93.5%)
60	74.7%	(57.8%, 85.7%)

Figure 8. Kaplan-Meier Curve for event Pump Replacement due to Pump Cause



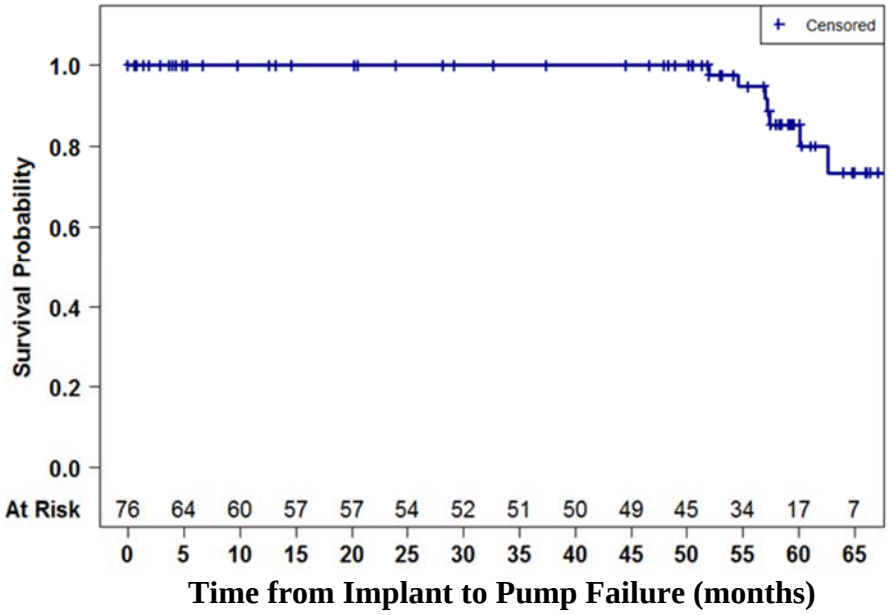
Pump failure is defined to be pump motor stall or premature battery depletion. There were seven pump failures: six due to pump motor stall and one due to premature battery ERI. Five of the six pumps with motor stall were replaced, and one death was adjudicated as related to pump motor stall.

Table 18 summarizes the pump time from implant to pump failure survival estimates. Figure 9 is a Kaplan-Meier curve of the data in Table 18. Table 19 summarizes the pump time from implant to pump failure survival estimates. Figure 10 is a Kaplan-Meier curve of the data in Table 19.

Table 18: Survival estimates for the event Pump Failure

Time from Implant to Pump Failure (Months)	Survival Estimate	Survival Estimate 95% Confidence Limits
50	100%	--
55	94.7%	(80.4%, 98.7%)
60	85.3%	(68.1%, 93.7%)
65	73.3%	(49.4%, 87.2%

Figure 9. Kaplan-Meier Curve for event Pump Failure



System Performance

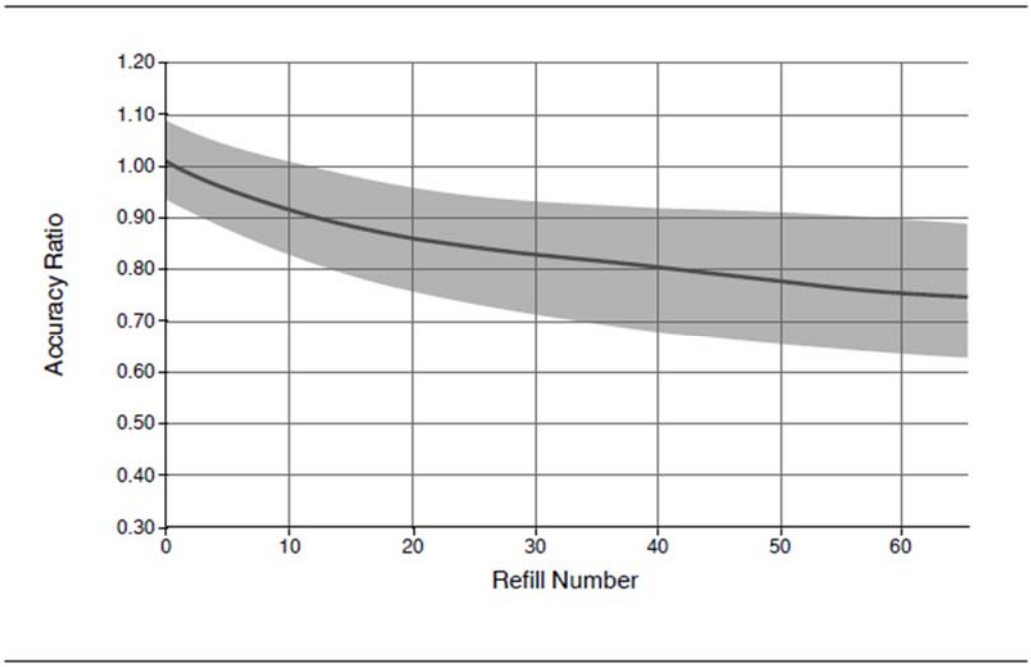
In the DelIVery for PAH clinical trial, a trend was seen of more drug removed from the pump at refill than expected (less drug delivered than expected). The ratio of actual versus expected drug delivered at refill (refill accuracy ratio) decreased as the number of refills increased. See Figure 6 for the DelIVery for PAH clinical trial flow rate accuracy data (refill accuracy ratio).

Based upon the accuracy ratio data from the study, it has been determined that over a period of time (months to years), the accuracy ratio of the ISR gradually decreases. The decrease is due to an equilibration of gas pressures within the motor chamber. The clinical data, mathematical modeling, and bench testing indicate that over the expected longevity of the pump, the accuracy ratio will decrease and plateau at approximately 0.8. The expected accuracy ratio of the ISR for a 40 mL refill volume is depicted in Figure 10.

Figure 10. Calculation of Accuracy Ratio

$$\text{Accuracy Ratio} = \frac{\text{Previous fill volume - Actual removed volume}}{\text{Previous fill volume - Expected removed volume}}$$

Figure 11. Implantable System for Remodulin® expected accuracy ratio for a 40 mL refill volume. The shaded area represents the DelIVery for PAH clinical trial refill accuracy data (95/95% tolerance interval of the exponential data model).



Clinical Study Conclusion

A total of 64 subjects were enrolled in the DelIVery for PAH study at 10 sites in the United States. Of these, there were 60 attempted system implants and all 60 were successful. There were 5 events that required catheter revisions. There were 7 events that required early pump replacement. This report represents a total of 120.7 years of cumulative follow-up in subjects implanted with the PAH Implantable Vasodilator Therapy (PIVoT) system.

The primary safety objective was analyzed with data as of June 13, 20113 and was met ($p<0.0001$). The observed rate of catheter-related complications per 1000 days of 0.27 with the system was significantly less than the rates observed in literature for a CVC system. These rates ranged from 1.05 to 2.51 per 1000 days. Therefore, the safety of the Model 10642 Implantable Intravascular Catheter has been demonstrated.

As expected, effectiveness variables including Quality of Life (QoL) (CAMPHOR and EQ-5D questionnaires), 6-Minute Walk, New York Heart Association Functional Classification showed little or no change when comparing the external pump (baseline) to the implanted pump; this was expected since the treatment therapy (Remodulin) is the same with the external and internal pumps.

Overall, the study objectives were met, demonstrating that the Model 10642, when used with the Medtronic SynchroMed II Implantable Infusion System to deliver Remodulin, is safe for patients with PAH.

2. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 11 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General Hospital and Personal Use Devices 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 DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The clinical study did not have an effectiveness endpoint. Device effectiveness is based on the device's ability to provide accurate drug delivery. The pump component of the ISR is the Synchromed II pump approved under P860004. The intravascular catheter is the new component of the ISR. The clinical study demonstrated the accuracy profile of the device throughout the course of treatment. In the DelIVery for PAH clinical trial, a trend was seen of more drug removed from the pump at refill than expected (less drug delivered than expected). The ratio of actual versus expected drug delivered at refill (refill accuracy ratio) decreased as the number of refills increased. Based upon the accuracy ratio data from the study, it has been determined that over a period of time (months to years), the accuracy ratio of the ISR gradually decreases. The decrease is due to an equilibration of gas pressures within the motor chamber. The clinical data, mathematical modeling, and bench testing indicate that over the expected longevity of the pump, the accuracy ratio will decrease and plateau at approximately 0.8.

B. Safety Conclusions

Remodulin is already approved for intravascular infusion via non-implanted infusion pumps. According to the approved drug labeling, Remodulin is a prostacyclin vasodilator indicated for:

- Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH

associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%)

- Patients who require transition from Flolan®, to reduce the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

The implanted Synchromed II pump is also an approved device (P860004). The new part of the device system is the intravascular catheter. The primary objective of the clinical trial was to demonstrate that catheter was safe for use when used with the Synchromed II to deliver Remodulin.

The primary endpoint for the clinical trial, catheter related complications per 1000 days, was met.

Data cut-off	Performance goal	Patient days	Catheter-related complications	Catheter-related complications per 1000 days	One-sided upper 97.5% confidence bound	P-value
June 21, 2013	Rate per 100 days < 2.5	22,013	6	0.27	0.59	<0.0001
January 11, 2017		89,935	7	0.08	0.16	<0.0001

The clinical trial also reported adverse events for the combined use of the device and drug. These are reported in the clinical summary.

The reliability of the implanted devices was also considered as part of the safety evaluation. The catheter and pump reliability were evaluated separately and are described in the clinical summary. Medtronic has agreed to conditions of approval to address failure modes that impact the reliability of the pump device.

C. Benefit-Risk Determination

The treatment effect is a function of the patient's response to Remodulin, which may vary over time and require titration of the drug dose. The device system is a drug delivery system and does not have an independent therapeutic effect.

The device system might improve the ability of the patient to be free of self-management of the pump and activity restrictions that may occur from having an external pump with an intravascular catheter. Therefore, all patients who receive this device system may be expected to gain this benefit. However, the requirement that all pump management (e.g., pump refills, troubleshooting any pump related issues, etc.) takes place at a specialty center rather than the patient's home may decrease the value of the probable benefit even though these factors would not be considered to be a risk. Patients should consider the probable benefits for their own specific situations.

The study was limited to patients with Class I, II, or III PAH. Patients with Class IV disease were specifically excluded. Therefore, patients with Class IV disease would not be indicated for the device and it is possible that patients with a progressive Class III disease should not be considered because of the risk that would arise when they reach Class IV because they may not be able to tolerate a sudden cessation of Remodulin therapy.

Patients with PAH who may be able to maintain a more active lifestyle may derive the benefit of having an implanted rather than an external pump. The specific type or duration of these activities was not identified in the study.

While the maximum duration of use of the ISR has not been determined, the longevity of the device is limited by the battery life. Battery life is inversely proportional to flow rate (e.g., higher flow rates result in shorter battery life). With respect to issues relating to the performance of the pump, pump stalls were reported during the study. The design of the pump has been modified to address motor stalls. Two pumps also experienced internal leakage causing the pump to fail between 4 -5 years of use, which is resulted in the death of one patient. As a condition of approval, the sponsor has added a warning to the labeling and will implement mitigations for this failure mode within 12 months of approval.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

D. Overall Conclusions

The data in this application support the reasonable safety and effectiveness of the Implantable System for Remodulin® for adult patients with Class I, II and III pulmonary arterial hypertension (PAH) receiving intravenous delivery of Remodulin.

XIII. CDRH DECISION

CDRH issued an approval order on 12/22/2017.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

The approval order included the following conditions of approval

1. ODE Lead PMA Post-Approval Study: The Office of Device Evaluation (ODE) will have the lead for this clinical study. You must conduct a prospective, open-label, multi-center evaluation of the PMA-approved, commercially-distributed Implantable System for Remodulin® (ISR) consisting of at least 50 US patients that receive the ISR post-approval. The effort should assess the rate of catheter-related complications and pump failures through five years for the RIS as used according to the labeled indications for use. The evaluation of patients at each patient follow-up visit should require that clinicians perform a review of the pump logs in addition to a standard interrogation since a review of the logs will provide more complete information on pump stalls and alarms. When appropriate or as requested by FDA, you should submit PMA supplements requesting approval to update your Instructions for Use (IFU) to include follow-up data from these trials.

2. Within 6 months of PMA approval, you must submit a report that contains a pump failure analysis of the root cause of internal pump tube kinking and leaking. In addition, within 12 months of PMA approval, you must implement effective mitigations to address this mechanism of device malfunction and submit the required documentation (e.g., PMA supplement).

3. Beginning at the time of market release, you have agreed to validate the initial training program (new system implant, follow-up and when to perform the catheter patency check) for the

Medtronic Implantable System for Remodulin® (ISR) utilizing the to-be-marketed user interface and training materials per a protocol that includes, but is not limited to, the following items:

a. The user groups will include naïve users (i.e., users with no previous experience on the Medtronic Implantable System for Remodulin®) from each of the following specified user groups:

    i. healthcare professionals involved in implanting the device
    ii. healthcare professionals involved in maintaining, programming, or refilling the device

b. Tasks to be included are critical tasks unique to ISR in the listed use scenarios. Tasks unique to ISR do not include those performed in the marketed SynchroMed II pump or as standard medical practice.

    i. pump preparation
    ii. therapy initiation
    iii. follow-up
    iv. surgical use
    v. dose accuracy checks
    vi. pump refill
    vii. when to perform the catheter patency check

c. The critical tasks will include all tasks that, if performed incorrectly, would or could cause serious harm to the patient or user, where harm is defined to include compromised medical care. The protocol will include a complete list of tasks for each scenario, and will designate which are critical tasks. Identification of critical tasks will include evaluation of incorrectly performed tasks that may result in dosing error or infection.

d. Acceptable validation of the training program will be based on the following

    i. An analysis of human factors validation test results with focus on any problems found during the testing. Problems are use errors and "close calls" on critical tasks observed by the test facilitators (observational data) and difficulties with use, including close calls, reported by the test participants (interview data).

    ii. For those use errors and problems that could result in serious harm, the test data should be analyzed to determine which part of the user interface was involved and how the user interaction could have resulted in the use error or problem.

    iii. An analysis of these data will describe any remaining residual use-related risk. Acceptability of this residual risk is then established based on a sound rationale that modifications to the user interface (including the device and the labeling) or the training program are unlikely to further reduce risk, are not practicable, and the remaining residual use-related risks are outweighed by the benefits derived from use of the device.

4. The following warning statements will be included in your labeling:

    a. During the pivotal clinical trial for the Implantable System for Remodulin®, 10% of patients experienced pump failures after 4 years of use. At least 33% of these failures occurring after four years of use resulted in the device failing to deliver Remodulin without corresponding error alarm. The remaining percentage of reported malfunctions occurred with a motor stall alarm that was reported by the patient. Patients who cannot tolerate a sudden cessation of Remodulin therapy may not be appropriate candidates for the Implantable System for Remodulin®.

    b. Patients with hearing loss may not be able to hear pump error alarms coming from the implanted pump, which may cause delay in therapy if the patient does not hear the alarm and contact the physician in a timely manner.

5. The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is also restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. The sale and distribution of this device are further restricted to the conditions prescribed, recommended or suggested in the approved drug labeling for Remodulin. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device 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.