

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208276Orig1s000

CLINICAL REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: March 13, 2015

From: Jessica D. Eisner, MD, General Hospital Devices Branch, DAGRID, ODE, CDRH

To: CDR Alan Stevens, Engineer, General Hospital Devices Branch, DAGRID, ODE, CDRH

Device Name P140032 - RIS – Remodulin Implantable System [SynchroMed implantable pump]

I. Issue

Provide a clinical review of the subject PMA submission.

The submission states that “Medtronic considers the use of the RIS as not significantly affecting the quality of the human environment. Use of the RIS is intended to be used in a manner in which waste will be controlled or the amount of waste expected to enter the environment may reasonably be expected to be non-toxic. As such, an environmental assessment has not been included in this PMA application.”

The Administrative Documents submitted as part of the submission states that “The Clinical Studies section of the PMA provides:

- The DelIVery for PAH Clinical Study report, MDT2055289 DelIVery for PAH PMA Report (G100017).
- Design differences between the DelIVery for PAH clinical study system and the RIS are provided.
- A complete list of centers, investigators, and IRBs is provided in MDT2055289 Appendix 6.3 of the DelIVery for PAH PMA Report.
- Death summaries are provided in MDT2055289 Appendix 6.12 of the DelIVery for PAH PMA Report.
- A copy of the Clinical Investigation Plan and change history”

Background:

Remodulin (treprostinil) Injection (NDA approval number 021-272)8 is a sterile sodium salt formulated for continuous subcutaneous or intravenous (IV) administration. Remodulin is an existing prostanoid therapy for treating PAH patients. Treprostinil sodium, the active ingredient in Remodulin Injection, is designated as an Orphan Product. With IV administration, Remodulin is administered via an external infusion pump and surgically placed central venous catheter. Remodulin is supplied in 20 mL vials in concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL, and 10.0 mg/mL and is diluted with 0.9% Sodium Chloride Injection or Sterile Water for IV administration.

Remodulin is currently FDA approved for the same patient population and route of delivery. The use of Remodulin in the RIS does not change the drug’s indicated patient population, drug dosage, formulation or route of administration for which the drug has already received FDA approval. Remodulin is marketed by United Therapeutics Corporation (UTC).

The submission states that UTC will submit an NDA supplement to add RIS to the Remodulin labeling for the undiluted 2.5 mg/mL, 5.0 mg/mL, and 10.0 mg/mL concentrations.

Remodulin Label (excerpts):

Indication: Remodulin is indicated for the 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%).

Adverse Events with Subcutaneously Administered Remodulin

Patients receiving Remodulin as a subcutaneous infusion reported a wide range of adverse events, many potentially related to the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). During clinical trials with subcutaneous infusion of Remodulin, **infusion site pain and reaction** were the most common adverse events among those treated with Remodulin. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment.

Other adverse events included **headache, diarrhea, rash, jaw pain, edema, vasodilatation and nausea**, and these are generally considered to be related to the pharmacologic effects of Remodulin, whether administered subcutaneously or intravenously. The safety of Remodulin was also studied in a long-term, open-label extension study in which 860 patients were dosed for a mean duration of 1.6 years, with a maximum exposure of 4.6 years. Twenty-nine (29%) percent achieved a dose of at least 40 ng/kg/min (max: 290 ng/kg/min).

The safety profile during this **chronic dosing** study was similar to that observed in the 12-week placebo controlled study except for the following suspected adverse drug reactions (occurring in at least 3% of patients): **anorexia, vomiting, infusion site infection, asthenia, and abdominal pain**.

Post-Marketing Experience

In addition to adverse reactions reported from clinical trials, the following events have been identified during post-approval use of Remodulin. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The following events have been chosen for inclusion because of a combination of their seriousness, frequency of reporting, and potential connection to Remodulin. These events are **thrombophlebitis** associated with peripheral intravenous infusion, thrombocytopenia bone pain, pruritus and dizziness. In addition, **generalized rashes**, sometimes macular or papular in nature, and **cellulitis** have been **infrequently** reported.

Overdose: Signs and symptoms of overdose with Remodulin during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.

II. Documents

P140032 and G199917

III. Review

Indications for Use:

The proposed indication for use for the Remodulin Implantable System is:

The Remodulin® Implantable System is intended for the chronic intravenous infusion of Remodulin® (treprostinil) Injection for use in the treatment of pulmonary arterial hypertension (PAH) in patients that are indicated for Remodulin®.

Principle of Operation: The submission explains that “Remodulin (the “drug”) enters the Remodulin Implantable System implantable infusion pump (the “pump”) through the reservoir fill port and passes through the reservoir over pressurization valve and into the pump reservoir. At normal body temperatures, propellant exerts pressure on the reservoir bellows which contains the drug. This pressure advances drug into the pump tubing. The battery-powered electronics and motor precisely delivers the programmed dose out through the catheter port and into the Remodulin Implantable System intravascular catheter (the “catheter”). The peristaltic action of the pump moves the drug from the pump reservoir, through the pump tubing, check valve, catheter port, and implanted catheter, to the infusion site.”

Device Description

The submission states that “the Remodulin Implantable System (RIS) is a programmable, implantable drug delivery system for chronic intravenous infusion of Remodulin in patients with Pulmonary Arterial Hypertension (PAH). The RIS, tools and accessories are described in this section along with the regulatory status of each component. The RIS being proposed for this PMA is depicted in Figure 1-1 and includes:

- Model 8201 Implantable Intravascular Catheter [**Not used during the clinical study**]
- Model 8637 SynchroMed II Programmable Pump for RIS (CFNs 8637P20 and 8637P40)
- Model 8840 N’Vision Clinician Programmer and Model 8870 Application Card including RIS software application

Remodulin Implantable System

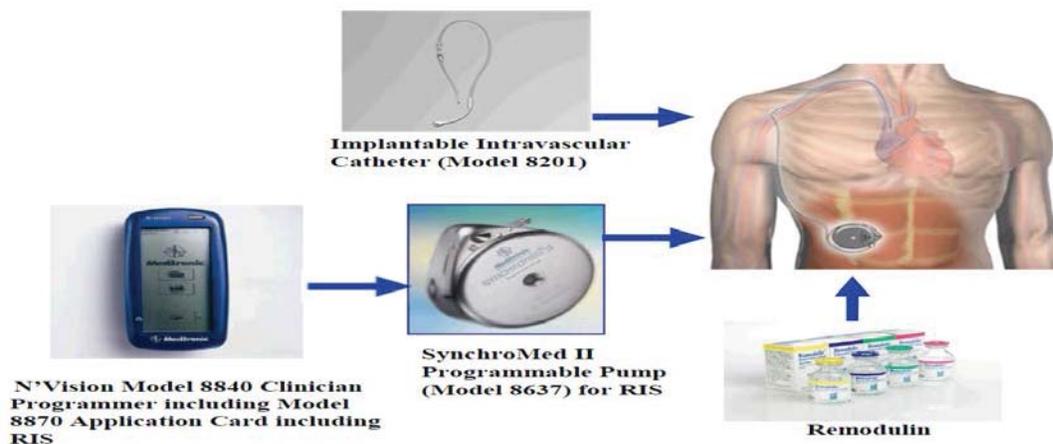


Figure 1-1: Remodulin Implantable System

Catheter: Reviewer comments: *Of significant note, the catheter that is being proposed for marketing in the RIS system (Model 8201) is not the same one that was used in animal or clinical studies (Model 10642). Note the excerpted portion of the Table below from the submission,*

Table 23-1: Design Differences between Clinical Study and Market Release Systems

Component	Clinical Study PIVoT System (G100017)	Subject of this PMA Remodulin Implantable System (RIS)
Catheter	Model 10642 Anchor sleeve (1 piece design) 80cm	Model 8201 Anchor sleeve (2-piece design) 80cm, 100cm and 120cm The catheter package includes the market-released strain relief sleeve component for optional use.
Pump	SynchroMed II Model 8637	SynchroMed II for RIS Model 8637 Modified from FDA approved Model 8637 SynchroMed II programmable pump (P860004) <div style="background-color: #cccccc; width: 100%; height: 40px; margin-bottom: 5px;"></div> <ul style="list-style-type: none"> • SMII pump for the RIS will have unique packaging and labeling <ul style="list-style-type: none"> ○ New system manual for the RIS specific application including a new indication for use ○ RIS package literature, including a new patient manual ○ RIS package labels with customer facing numbers 8637P20 or 8637P40

Model 8201 will be described first

The PMA submission states the following: “The Model 8201 Implantable Intravascular Catheter: The Model 8201 Implantable Intravascular Catheter (Figure 1-2 below; pasted from submission) consists of a 2-piece design: a catheter body segment and a pump segment. Drug will be dispensed from the RIS pump into the patient’s vasculature via the Medtronic Model 8201 Implantable Intravascular Catheter that is available in three lengths appropriate to the patient’s anatomy. Catheter lengths of 80, 100 and 120 cm include both the catheter body and pump segments. The catheter body segment is new and contains the catheter tip, which is placed in the superior vena cava. The pump segment is the FDA approved sutureless connector which connects the catheter body to the pump.”

Reviewer comments: *The design and use of the sutureless connectors throughout the clinical trial appears to have changed regularly. The submission states that the sutureless connector was developed by Medtronic and originally FDA approved under P860004/S81 March 22, 2006. The go on to explain that there were recently approved with design changes under P860004/S136 on December 15, 2011 [i.e. 5 months after the start of the clinical trial) and P860004/S167 on February 17, 2012 [i.e. almost 2 years after the start of the clinical study].*

The Sponsor goes on the state that the Model 8201 catheter [not used during the clinical study] will include the most recently approved sutureless connector design. The redesigned sutureless connector was submitted as a change to the clinical study Model 10642 catheter (G100017/S032, accepted May 8, 2013 [i.e. 6 months after the last patient enrolled in the clinical trial]).



Figure 1-2: Overview of the Model 8201 Catheter with Catheter Body Distal End Detail

The submission states that the catheter is made of radiopaque silicone with enhanced radiopacity at the distal tip. The submission states that “the Model 8201 catheter is similar to other Medtronic intravascular and intrathecal catheters except for the one-way valve at the distal end, metal coil reinforced catheter body and soft distal, closed catheter tip.” Also included in the catheter package:

- Market released vein pick (P/N 103548) will be included as an optional implant tool.
- An additional market-released sleeve will also be included in the package for strain relief as an optional component.

The following Table 1-6 {below} has been pasted from the submission; it lists the components for the catheter Model 8201 (which was not used during the clinical study but is being proposed for marketing).

Table 1-6 provides the list of catheter body materials and identifies any tissue, blood and/or drug contact.

Table 1-6: Catheter Body Component Materials

Component Part(s)	Tissue/Blood/Drug contact	Model 8201 (subject of this PMA)
Anchoring Sleeve	Tissue	(b) (4)
(b) (4) Retention Sleeve	Tissue	(b) (4)

Component Part(s)	Tissue/Blood/ Drug contact	Model 8201 (subject of this PMA)
		(b) (4)
		(b) (4)
Catheter Tip and Connector Sleeve	Tissue, blood, drug	(b) (4)
		(b) (4)
Sleeve Valve	Blood, drug	(b) (4)
		(b) (4)

The following Table describes how the Model 8201 catheter has been designed to mitigate the risk of certain issues. There is no comparative Table for the Model 10642 catheter that was used in the clinical trial.

(b) (4)

The submission states that “Model 8201 implantable intravascular catheter is new. An evaluation of biocompatibility and biostability was performed to demonstrate that the components of the catheter are biocompatible and biostable. The biological evaluation, including exhaustive extractions and toxicological assessments demonstrated compliance of the materials used in the Model 8201 implantable intravascular catheter with ISO 10993-1. All catheter 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.”

The Sponsor has also submitted an extensive table of “Catheter Design Verification” performance testing for the Model 8201 catheter; the submission claims that the Model 8201 catheter passed all of these tests. There is no such table or comparison for the Model 10642 that was used in the clinical studies. Instead the Sponsor submitted a Table (see Appendix A) which compares “Market Release Catheters to the Model 8201” – but does not include the Model 10642 used in the clinical study in this chart.

As to Model 10642, the submission explains that “The versions of the devices (Model 10642 catheter and Model 8637 pump) used in the animal study was the same design iteration used in the clinical study. These devices share the same primary design, materials and similar manufacturing processes as the RIS, however the Model 8201 catheter has an updated anchor sleeve and offers additional lengths. The Model 8637 pump for RIS has been configured to communicate exclusively with the RIS software application.”

Reviewer Comments: No engineering figures of the Model 10642 catheter used in the study are presented in the current submission; nor is there a feature comparison table between Model 10642 and Model 8201. In addition, none of the clinical studies were performed using this catheter model. This, as it related both to patient safety and the pre-determined safety endpoints that were analyzed in this study will be further discussed later in the submission.

Catheter – continued – Model 10642 – used in the clinical study:

Model 10642 Implantable Intravascular Catheter (with sutureless connector) The Model 10642 Implantable Intravascular Catheter is designed to be connected to the SynchroMed II Implantable Infusion System. The catheter is used with the currently available Medtronic sutureless connector. For purposes of this clinical study, the catheter tip is intended to be positioned in the superior vena cava, and to deliver the drug systemically and continuously. Table 2 (pasted from the submission) indicates the features of the Model 10642 Catheter.

Table 2: Model 10642 Catheter - Key Features	
Feature	Model 10642
Catheter tip	Silicone tip-closed end
Distal exit site	Side holed with one-way valve
Connector	Custom sutureless connector to SynchroMed II pump
Catheter body	Radiopaque Silicone
Proximal catheter body	Coil reinforced silicone
Length	80 cm
Stabilization/ Fixation	Suture sleeve
Introducer size	8 French
Catheter lumen volume	180 uL (2.2 uL/cm)

Study Design and Protocol (per the PMA submission):

Overview:

- Prospective, single arm, non-randomized open label study
- 10 US sites, up to 70 subjects
- A minimum of 22,000 subject follow-up days were necessary to evaluate the end point–
- Study procedures: Screening [PE, blood collection, pregnancy test, walk test, NYHA classification, QoL and AEs] (see Appendix B for full schedule)
- Study visits:
 - Scheduled: Baseline, implant, Weeks 1 & 6, Months 3, 6, 12, & then q 6 mos. until end
 - Unscheduled (*i.e.*, pump refill, dose change, AE)
- Average time between refills is ~6-8 weeks
- Study Duration: The expected study duration is approximately 28 months. Study subjects will be followed until approval is granted from a regulatory body, or official study closure.

Protocol:

The purpose of the clinical trial was to evaluate the safety profile of the Model 10642 Implantable Intravascular Catheter, a component of the PAH Implantable Vasodilator Therapy (PIVoT) system. The clinical study was 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.

Subjects: The study is expected to enroll up to 70 subjects to ensure at least 50 subjects are successfully implanted. **Reviewer comment:** *This goal was achieved.*

Inclusion Criteria

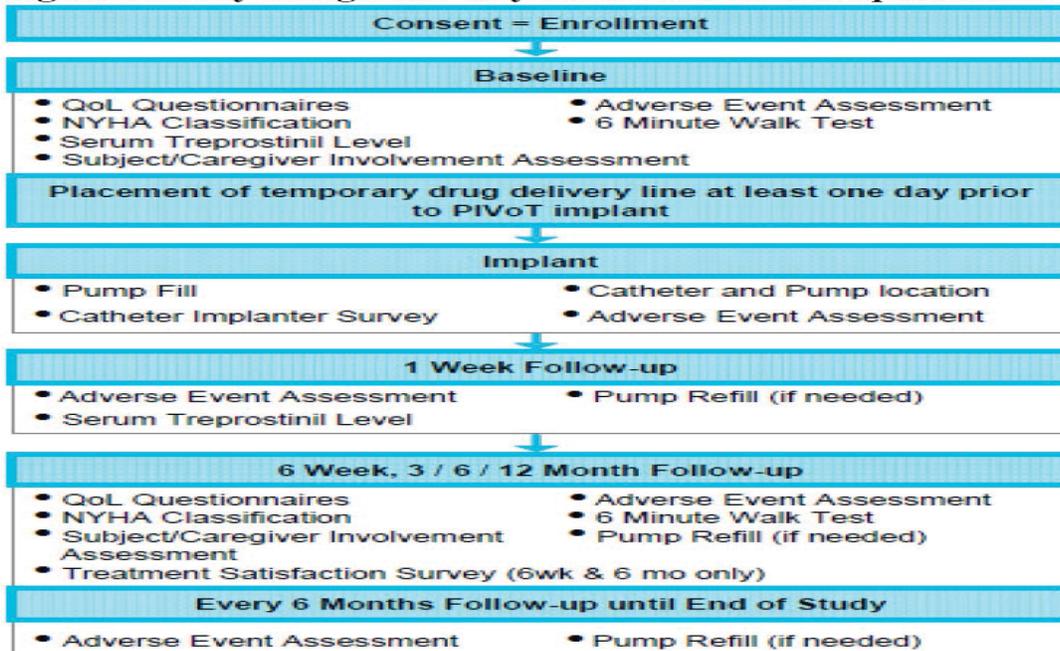
- 18 years of age or older
- able to provide written informed consent
- able to comply with the protocol, including required follow- up visits
- diagnosed with Pulmonary Arterial Hypertension (World Health Organization (WHO) Category Group 1 [by the WHO Clinical classification system])
- Receiving continuous infusion of Remodulin therapy via IV using an external pump system. Patient on stable Remodulin dose (no change in dose) for at least 4 weeks
- Anticoagulation therapy can be managed to permit safe device implantation
- No history of pulmonary embolism since the initiation of subcutaneous or IV therapy for PAH

Exclusion Criteria

- Pregnant, nursing, or of child bearing potential and 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.
- Initiated on a new oral PAH therapy in the last two months
- Recent (within three months) or otherwise unresolved infection requiring Abx treatment

- Diagnosed with PAH associated with hemoglobinopathies , HIV, schistosomiasis, portal hypertension, pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis
- Implanted with electrical stimulation medical devices(s) anywhere in the body (e.g., cardiac pacemakers, implantable cardioverter defibrillators (ICDs), spinal cord stimulators).
- 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
- Has an existing external catheter(s) that would remain in place after the pump implant
- Implantable pump cannot be implanted 2.5 cm or less from the skin surface
- Body size is not sufficient to accept implantable pump bulk and weight
- Has increased susceptibility to systemic or soft tissue infections
- Patient is Functional Class IV (*New York Heart Association (NYHA)*)

Figure 1 Study Design and Key Data Collection Requirements



Endpoints:

The stated primary objective of the clinical study was to demonstrate that the Model 10642 Implantable Intravascular Catheter was safe when used with the Medtronic SynchroMed II Implantable Infusion System to deliver Remodulin. The endpoint of this objective was catheter-related complications per 1000 patient days.

The ancillary objectives were:

- To characterize % change of six-minute walk test distance from baseline to 6 wks post-implant
- To characterize changes in quality of life

- To characterize the incidence of adverse events
- To characterize healthcare utilization (hospitalizations, emergency room visits, & urgent clinic visits)
- To assess pump fluid delivery accuracy
- To assess subject/caregiver involvement in system management
- To characterize plasma treprostinil concentration change

Review of Data and Results in PMA submission:

Demographics (cut & pasted from the PMA submission)

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

The Sponsor explains that the average age of the enrolled subjects, was 50.1 ± 13.5 years. Women represented 80% of the total subjects enrolled in the study, which was expected since the prevalence of women among those diagnosed with PAH in the general U.S. population is approximately 78%. One subject was enrolled and exited prior to fully completing the baseline visit. This subject only had demographic data collected. Therefore, data from only 63 subjects are included in most of the tables.

Reviewer comment: Agreed with Sponsor’s presentation & assessment of age/gender data and conclusions.

Demographics continued (Table below cut & pasted from submission)

Subject Characteristics	Non-implanted Subjects (n = 4)	Implanted Subjects (n = 60)	Total Subjects (n = 64)
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%)

Reviewer comment: The Sponsor does not comment on the racial aspects of demographic distribution. It is noted that not many South East Asian or African Americans were included

in the study. In particular South East Asians and African Americans appear to be under represented. This could also be an issue in regards to the refill procedure as it could be more difficult to perform refills in darker skinned individuals; in addition, darker-skinned South East Asians, African Americans and Latinos have a higher tendency to produce keloid scarring. Please justify how the study population reflects the racial and ethnic diversity of PAH patients in the US and explain who they will all be able to access and utilize the RIS system.

Pneumonia	0 (0%)	7 (12%)	7 (11%)
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Reviewer comment: *Please provide justification for why 7 patients were enrolled into the study with pneumonia at baseline. Please also explain whether these same seven patients experienced excessive infections or other adverse events during the study.*

Review comments: *The baseline Cardiac History for the patients in the study is indecipherable and not possible to place into proper context. It appears as though approximately 9 (minimum) – 15 (maximum) patients had rhythm disturbances upon entering the study (from the baseline cardiac characteristics). However, from the presentation of the data the baseline cannot be determined as one patient may have more than one type of arrhythmia; please characterize the arrhythmia data so that it indicates how many patients (N and %) had history of an arrhythmia upon study entry; also compare this to the number (N & %) observed during the study and explain how the risk of arrhythmias is minimized for implantation (since this and other cardiac AEs can obviate the presumed benefits of the RIS system if they prove to be fatal or life threatening). Analyze the cardiac rhythm-related adverse events in the study with what was present at baseline and what would be generally expected in the PAH population.*

Study Exits (not-due to Death): Four subject exits that occurred prior to implant. No subjects have exited post-implant (with the exception of the five subjects who died post-implant)

Table 16 Pre-implant Study Exits

Subject	Days after Enrollment	Study Exit Description (Verbatim from Case Report Form)
(b) (6)	0	Patient is a person whose body size is not sufficient to accept implantable pump bulk and weight
(b) (6)	11	Worsening on last C-MRI - No RHC in a year - No experience with Patient with dose >140 NKM
(b) (6)	57	Patient was scheduled for implant procedure on (b) (6) but developed Hickman Catheter Infection on (b) (6)
(b) (6)	85	Subject contracted two PICC line infections while on IV Remodulin. After much deliberation, subject ultimately decided to withdraw from study and return to SubQ therapy.

Study Deaths: There were five deaths that occurred during the trial. These deaths were reviewed by the Adverse Event Advisory Committee (AEAC), and all were adjudicated as not related to the investigational system.

Reviewer comment: *The SAE report forms and narrative of these deaths were reviewed; the adjudication of the Death events appears acceptable.*

Study Implant information (table below pasted from the submission):

Category (n,%)	Implanted Subjects (n = 60)
Implant Side	
Left	25 (41.7%)
Right	35 (58.3%)
Pump Model	
8637-20 ³⁴	1 (1.7%)
8637-40 ³⁵	59 (98.3%)
Catheter Introduction Vein	
Axillary	2 (3.3%)
Cephalic	35 (58.3%)
Internal jugular	6 (10.0%)
Subclavian	17 (28.3%)
Initial Remodulin Concentration	
10.0 mg/mL	59 (98.3%)
5.0 mg/mL	1 (1.7%)
Pump Orientation	
Lateral	20 (33.3%)
Medial	40 (66.7%)
Implant Time (minutes)	
Mean ± Standard Deviation	102 ± 32
Median	98.5
25th Percentile - 75th Percentile	79-120
Minimum – Maximum	47-184

Reviewer comment: *It is noted that only one patient received the Model 8637-20 pump (20 ml pump).* (b) (4)

Safety:

The submission states that “the AEAC adjudicated all adverse events in the trial.” and “that the AEAC consists of a minimum of three non-Sponsor employed physicians, including an AEAC chairperson. At least three AEAC members must adjudicate, at a minimum, all deaths, serious AEs, and AEs related to any component of the system under investigation and/or Remodulin Injection. All other AEs will be adjudicated by at least one physician member of the AEAC composition of the DMC was complete with a total of three members.” The list of the AEAC meetings has been pasted below (Table 12 - from the submission).

Table 12 AEAC Committee Meetings

Meeting Date	Events Adjudicated ¹¹
October 2, 2010	0 ¹²
June 6, 2011	0 ¹³
August 8, 2011	2 ¹⁴
October 17, 2011	10
January 9, 2012	11
February 21, 2012	20
April 16, 2012	36
June 13, 2012	39
August 20, 2012	34
October 1, 2012	52
November 26, 2012	115
February 4, 2013	41
February 26, 2013	18
May 6, 2013	68
July 22, 2013	64
August 12, 2013	29
November 18, 2013	64
January 16, 2014	35
February 13, 2014	1
March 3, 2014	22
May 6, 2014	31
July 28, 2014	55
August 14, 2014	34

Reviewer comments: *It is noted that nearly one-third of all AEs in the clinical study for this PMA's two-year long clinical study were adjudicated on a single day (November 26, 2012). What were the quality control or quality assurance processes in place to ensure that time constraints and the (non-voting) presence of the Primary Study PI did not adversely impact AE review and adjudication?*

Adverse events were to be classified according to related, as is described in the table below (Table 79 pasted from the submission).

Table 79 Adverse Event Classification

Relatedness	
Procedure related	An adverse event that occurs due to any procedure related to the implantation or surgical modification of the system
Refill process-related	An adverse event that results from the process of refilling the implantable drug infusion pump
Catheter patency test-related	An adverse event that results from performing the catheter patency test
Catheter-related	An adverse event that results from the presence or performance (intended or otherwise) of the Implantable Intravascular Catheter, Model 10642
Drug-related	An adverse event that results from the presence or performance (intended or otherwise) associated with the use of the drug (Remodulin Injection). This includes all cases of lack of efficacy, overdose, drug abuse and misuse, drug maladministration or accidental exposure and dispensing errors. It also includes all cases of drug-drug interaction
Infusion pump-related	An adverse event that results from the presence or performance (intended or otherwise) of the Implantable Drug Infusion Pump
CAP kit-related	An adverse event that results from the presence or performance (intended or otherwise) of the CAP kit.
Programmer-related	An adverse event that results from the presence or performance (intended or otherwise) of the programmer
Implant Tool-Related	An adverse event that results from the presence or performance (intended or otherwise) of the implant, introduction, or tunneling tool

The following (Table 78) defines catheter related events.

Table 78 Guidance Definitions for Catheter-Related Events specific to the Model 10642 catheter

Event	Definition
Model 10642 Catheter Disconnect	A clear separation of the junction between the Model 10642 catheter and sutureless connector (see Figures 1 and 2), with confirmation via radiographic or fluoroscopic imaging with or without evidence of Remodulin Injection subcutaneous catheter leakage and/or pump reservoir septum leakage (i.e., local site reaction to Remodulin Injection with symptoms such as erythema, tenderness, edema). Adverse event also may meet the subcutaneous catheter leakage definition
Catheter Connector-Pump Disconnect	A clear separation of the junction between the sutureless connector and the catheter port of the SynchroMed II pump, with confirmation via radiographic or fluoroscopic imaging with or without evidence of Remodulin Injection subcutaneous catheter leakage and/or pump reservoir septum leakage (i.e., local site reaction to Remodulin Injection with symptoms such as erythema, tenderness, edema). Adverse event also may meet the subcutaneous catheter leakage definition.
Model 10642 Catheter Dislocation/Dislodgment	Clinically meaningful movement or displacement of the intravascular (central venous) end of the catheter from the location of implant as indicated by radiographic or fluoroscopic image.
Model 10642 Catheter Occlusion	A Remodulin Injection under dose (i.e., increased symptoms of PAH and/or decreased side effects of Remodulin Injection), and a plasma treprostinil level at least 80% less than expected level (utilizing baseline plasma level or 1 week plasma level, whichever is most recent, if dose is unchanged, otherwise utilizing McSwain regression equation) in the setting of normal pump performance and a catheter patency test result of either: (1) a pressure greater than 400mmHg or (2) an increase in syringe volume. Note: A catheter kink is considered as one possible cause for occlusion

Event	Definition
Model 10642 Catheter Breakage	Direct visual or radiographic evidence of inner catheter tubing separation or radiographic evidence of catheter coil separation (fracture): <ul style="list-style-type: none"> o Catheter embolism= radiographic evidence of disconnected portion of catheter which has moved from the implant location through the circulation (e.g., into or through the right atrium)
Bloodstream Infection (BSI)/ Sepsis	A blood stream infection that meets the conditions in one (1) of the following criteria: <p>Criterion 1</p> <ul style="list-style-type: none"> o Isolation of one or more recognized bacterial or fungal pathogens from one or more blood cultures (e.g., Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Klebsiella, Proteus, Salmonella species, Candida albicans). o The patient has at least one of the following signs and symptoms within 24 hours of a positive blood culture being collected: <ul style="list-style-type: none"> o Fever (>38°C); o Chills or rigors; or o Hypotension <p>Criterion 2</p> <ul style="list-style-type: none"> o Diagnosis of systemic infection by the surgeon or attending physician
Site Infection	At least one of the following: positive wound site culture, local erythema, tenderness, induration, or exudate at site, combined with initiation of antibiotic treatment. A positive blood culture could indicate sepsis (BSI- see above) and not site infection.
Pneumothorax	A collection of free air in the chest outside the lung whether or not the lung has collapsed. Definitive diagnosis is by chest X-ray, or in an extreme emergency, by clinical findings.
Venous Phlebitis and/or Thrombosis	If the pneumothorax is deemed procedure or catheter-related, it will contribute to the primary endpoint. Venous phlebitis: Inflammation of a vein with or without symptoms of pain, tenderness, erythema along the course of the vein. Venous thrombosis: Formation or presence of a blood clot in a vein, as verified by ultrasound

Event	Definition
Subcutaneous Catheter Leakage	Evidence of a local site reaction to Remodulin Injection (i.e., localized symptoms of erythema, tenderness, edema) along the subcutaneous catheter tract that is not associated with pump refill leakage. If adverse event also meets the Model 10642 Catheter Disconnect or Model 10642 Catheter Breakage definition, classify accordingly as disconnect or breakage.

Reviewers comments: According to various document submitted under the IDE for this combination drug-device study, the Table above was created to define the catheter –related events which would be used to calculate the safety endpoint (see Table 78 below). However, throughout the IDE process and the pre-PMA submission process it has been documented that ALL system complications will be considered in the device evaluation process. In addition, risk-benefit will be assessed looking at the totality of the data – not just the pre-specified events. Noted again here is the fact that this study was designed around the Model 16042 catheter (which utilized one anchor sleeve and two sutureless connector components for this trial).

Adverse event Evaluation:

The submission states that there were 737 AEs reported during the study and all AEs were reported throughout the study. Documented pre-existing conditions were not considered AEs unless the nature or severity of the condition had worsened.

The Sponsor states that there were 22 pre-implant AE’s in the study. 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.

Reviewer comments: The 22 pre-implant AEs were reviewed. All of them appear to be obviously unrelated to any RIS component or procedure. However, a few of these AEs beg questions about the conduct of the trial. Specifically, was the patient who had Klebsiella bacteremia allowed to proceed with receiving the implant? Also did the patient who tested positive for urine leukocyte esterase go on to test negative for this before proceeding with the implant procedure? These are two instances which could set a patient up for and AE or implant failure due to infection.

The submission goes on to list “unavoidable” events; an event was considered unavoidable if the onset and resolution occurred within the specified timeframe.

Table 46 Unavoidable 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

Per the submission (see Table pasted below), there were 20 unavoidable adverse events following the 60 implants.

Table 51 Unavoidable Adverse Events

Adverse Event Preferred Term	Number of Events (Number of Subjects, % of Subjects)	
	Events	Complications
Implant site pain	4 (4, 6.7%)	0 (0, 0.0%)
Nausea	4 (4, 6.7%)	0 (0, 0.0%)
Procedural vomiting	4 (4, 6.7%)	0 (0, 0.0%)
Incision site pain	2 (2, 3.3%)	0 (0, 0.0%)
Insomnia	2 (2, 3.3%)	0 (0, 0.0%)
Pyrexia	2 (2, 3.3%)	0 (0, 0.0%)
Musculoskeletal discomfort ⁵²	1 (1, 1.7%)	0 (0, 0.0%)
Musculoskeletal pain ⁵³	1 (1, 1.7%)	0 (0, 0.0%)

The Sponsor then states that “Following the 60 implants, there were 713 post-implant adverse events, 20 of which were unavoidable.”

Reviewer comments: The definition of unavoidable events is acceptable; however, in presenting the actual PMA data, no timeframes are given for these events to ascertain whether they met the defined requirements. The AEs were also not discussed in the context of the entire implant procedure and how this impacts the risk-benefit of the Remodulin Implantable System.

Discussion with the Agency agreed upon a set of “Catheter-related Events specific to the Model 16042 catheter” (see Table 79 which has been cut & pasted above). Subsequently, the submission goes on to present all of the events which they deemed to be “Catheter-related Events specific to the Model 16042 catheter”. These are presented below in Table 36 as “Primary Endpoint Events”.

Table 36 Primary Endpoint Events

Subject ID	Days post-implant	Preferred Term	AE Description
(b) (6)	0	Pneumothorax	It was noted that the surgeon had venous access difficulty during the implant procedure. Following the procedure the subject got up to go to the bathroom and reported shortness of breath. A chest x-ray showed a large left pneumothorax. A chest tube was inserted.
	7	Device dislocation	On (b) (6) the subject hyperextended her arm. The catheter slid into the intraclavicular region and the subject reported pain, erythema and swelling at the catheter insertion site (left clavicle), left neck, and left shoulder. She also reported pain radiating down her left arm. System modification performed on (b) (6).
	42	Device dislocation	On (b) (6) the subject complained of non-radiating stabbing pain in her left abdomen above the implanted pump, which was exacerbated with movement or sitting up. It was noted that the left abdomen was swollen above the implanted pump. The subject's left upper quadrant was tender with palpation. Abdominal CT scan showed pump and catheter in subcutaneous tissue of left abdomen. Admitted to hospital on (b) (6). System modification done on (b) (6).

Subject ID	Days post-implant	Preferred Term	AE Description
(b) (6)	22	Device dislocation	On (b) (6) the subject's recliner chair broke and caused her to fall backwards. She did not have any assistance and pulled / strained herself trying to get out of her chair. On (b) (6) she contacted the site and complained of muscle soreness and fatigue. On (b) (6) the site contacted the subject and she reported abdominal soreness and noted that the area near the pump had "a little redness". The subject refused to come in to be seen. On (b) (6) the site contacted the subject and she stated that the redness was worse. She noted that it "had spider web and a lightning streak above her pump site". The subject was advised to come in for assessment. On (b) (6) fluoroscopy was used to image pump and catheter. The catheter was found completely in the abdominal pocket.
	338	Device damage	On (b) (6) the subject reported soreness and inflammation at pump site (lower right abdomen) that had decreased but persisted for two weeks. The subject's last refill was on (b) (6) and the subject denied any fever, discharge, heat from site, or worsening of PAH symptoms. Fluoroscopy was utilized to image pump system integrity and the PI believed the system was intact. In August the subject was evaluated by Dermatology and Infectious Disease. On (b) (6) the subject's pump/catheter was explanted due to possible catheter leak and site pain. A new system was implanted on the left side with no complications. The explanted catheter was found to have been damaged (punctured).
	1021	Device damage	On (b) (6) the subject had a difficult refill. After three attempts were made, some redness was noted. After two additional attempts, the redness appeared to spread. At that time, fluoroscopy was requested and the catheter appeared to be in front of pump. The site accessed the pump under fluoro & completed the refill. The subject denied any worsening PAH symptoms including SOB, dyspnea, headache, flushing or chest pain. Following the refill, no systemic symptoms were reported but the subject continued to have site pain and redness. On (b) (6) the subject's pump/catheter was explanted due to possible catheter leak and site pain. A new system was implanted on the left side with no complications. The explanted catheter was found to have been damaged (punctured).
(b) (6)	187	Venous stenosis	On (b) (6) the subject notified the coordinator of a new onset of right upper extremity edema, which began in the right hand on the evening of (b) (6). By the morning of (b) (6) it had extended to the upper arm. On the afternoon of (b) (6) the subject saw her PCP for a regularly scheduled apt. The PCP ordered venous doppler studies, which were completed on (b) (6) and were interpreted as negative. On (b) (6) the subject called the study coordinator to report the edema was worsening. She also now reported some pain with the increased swelling and noted intermittent temperature and color changes in fingers of right hand. The subject was brought to clinic for evaluation and admitted to the hospital for further workup. The final diagnosis was "Stenosis at the junction of the right subclavian vein-SVC".

Subject ID	Days post-implant	Preferred Term	AE Description
(b) (6)	0	Pneumothorax	Following the implant procedure the subject was transferred to the PACU where she was noted to be dyspneic (oxygen saturations in the 80s), hypotensive (SBP in the 80s), and in severe pain. A chest x-ray was obtained and a modest right pneumothorax was seen. The subject was treated with supplemental oxygen (100% non-rebreather mask), fluid bolus, and IV Dilaudid for pain.

However, later in the adverse event section of the submission the test states that “a system-related adverse event” is defined as an adverse event related to one or more of the systems components: the catheter, pump, and programmer. Table 53 (cut & pasted below) lists these events and states there were 16 system-related (pump or catheter) adverse events occurring in the study. There were no events deemed related to the programmer.

Table 53: Post-Implant System-related Adverse Events

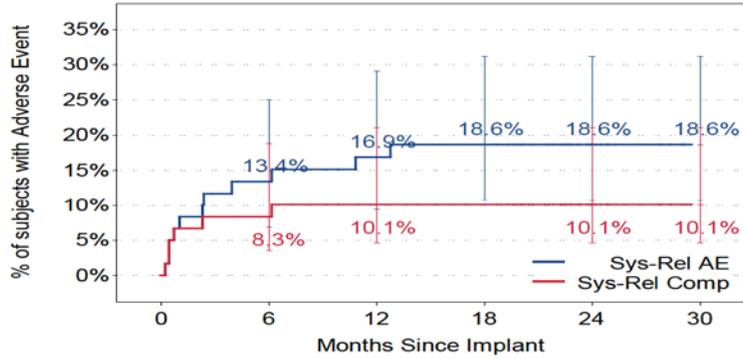
Adverse Event Preferred Term	Number of Events (Number of Subjects, % of Subjects)	
	Events	Complications
Device dislocation ¹	4 (3, 5.0%)	3 (2, 33%)
Implant site extravasation	3 (3, 5.0%)	3 (3, 5.0%)
Device damage ²	2 (1, 1.7%)	2 (1, 1.7%)
Venous stenosis	1 (1, 1.7%)	1 (1, 1.7%)
Abdominal pain lower	1 (1, 1.7%)	0 (0, 0.0%)
Abdominal pain upper	1 (1, 1.7%)	0 (0, 0.0%)
Dermatitis contact	1 (1, 1.7%)	0 (0, 0.0%)
Medical device pain	1 (1, 1.7%)	0 (0, 0.0%)
Muscle spasms	1 (1, 1.7%)	0 (0, 0.0%)
Skin striae	1 (1, 1.7%)	0 (0, 0.0%)
Total	16 (11, 18.3%)	9 (6, 10.0%)

Figure 16 from the submission shows the timing of the first system-related adverse event and first system-related complication excluding the unavoidable adverse events. The estimated rate of system-related complications at 6 months post-implant is 8.3% (95% confidence interval: 3.6%-18.9%).

1 This includes three events for catheter dislodgement in two subjects and one event of “pump flipped in pump pocket”.

2 This includes two instances of catheter damage/puncture in one subject.

Figure 16 Time to First Post-implant System-related Adverse Event Excluding Unavoidable AEs



	0	6	12	18	24	30
Number Remaining Sys-Rel AE	60	50	47	46	20	7
Number Remaining Sys-Rel Comp	60	53	51	51	21	8

Then there is Table 50 (cut & pasted from the submission and presented below) which lists the “AEs occurring during Implant”. Note that the Table does not indicate the patient ID number.

Table 50 Adverse Events Occurring During Implant – Relatedness Summary

Preferred Term	Complication Observation	Description (Verbatim from CRF)	Actions Taken	Relatedness
Atrial fibrillation	Complication	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. Weingarten 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	Observation	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)

Later in the submission, the following Table appears. This Table (61 – cut & pasted from the submission) lists “Implant/System Modifications Procedure-Related Infections”.

Table 61 Implant/System Modification Procedure-Related Infections

Subject ID	Days post-implant	Preferred Term	AE Description
(b) (6)	5	Bronchitis	On (b) (6) 5 days post implant, the subject reported fevers (temperatures up to 102.4), headache, productive cough, and muscle aches. A chest xray was done at the subject’s primary care providers office. Per the subject’s report, LLL bronchitis was observed. The subject was started on Zithromycin for 5 days. The event resolved on (b) (6)
(b) (6)	21	Legionella Pneumonia	On (b) (6) the subject was admitted to the ICU, diagnosed with pneumonia, altered mental state, and low potassium and developed sepsis from the pneumonia. On (b) (6) the subject developed renal failure secondary to septic shock. On (b) (6) the subject was diagnosed with legionnaire’s disease. The subject was discharged from the hospital on (b) (6) when the pneumonia was considered resolved.
(b) (6)	23	Pump Pocket Infection	The subject reported on (b) (6) having swelling and blotchy erythema around the pump pocket area, without tenderness. The subject continued to be monitored at visits. A system modification was completed on (b) (6) to change out only the sutureless connector, due to a suspected leak. The pump was repositioned and cultures were taken with 2 out of 3 testing positive for staphylococcus lugdunensis. On (b) (6) the subject reported that symptoms had resolved.
(b) (6)	1065	Sepsis	On (b) (6) 15 days post system modification, the subject reported pain at the pump site & the left shoulder. The subject had a temperature of 102, was hypoxic, and on exam, both of the sites appeared inflamed and fluctuant. The subject described tenderness at both sites. A full system explant was performed on (b) (6) The subject was discharged from the hospital on (b) (6) and the subject completed the IV and oral antibiotics at home. When the site contacted the subject on (b) (6) the subject reported having no symptoms and will be seen for follow-up in October.

Reviewer comments: Analysis of safety data is a complex process – even when data are presented clearly and in a sortable data format which allows independent analysis. However, this data – from a mere 60 patients- is presented in a way that seems to intentionally obfuscate analysis and comprehension. For example: it is not clear why several of the “system-related adverse events” (e.g. device dislocation, device damage, venous stenosis) are not considered “catheter related” and were not captured or discussed in the analysis of the primary endpoint or relation to the primary endpoint. Also the AE PT “device damage” is confusing at best, and misleading at worse since it is not clear that the device was itself damaged. Finally, in Figure 16 shown above, not only is the distinction between a ‘Sys-Rel AE” and a “Sys-Rel Comp” not clear, but the % of subjects with AEs appears to be higher than reported. However, there is no clear discussion of this to aide with elucidation.

Safety discussion:

Reviewers Comments: The presentation of safety data in bundles of separate categories or in tables with confusing and mixed categories is sub-optimal for analysis. The quality of AE

capture and coding in this PMA submission is unacceptable; it difficult to naviagte and it is difficult to determine if all AEs have truly been captured and validate the coding. For example, in Table 80 which lists of “all 737 AEs in the study” [presnted by the Sponsor on page 24-184 of Volume 24 of the Original Clinical study report], the entire narratives are caputred in the description box (instead of just a single verbatim term). Also, this extremely long table is not numbered so there is no way to ascertain the number of rows in the table short of manually counting them.

In addition, the information in Table 80 is lumped together in a way that is nonsensical from a safety standpoint. It is also not clear why AEs – including SAEs- are categorized as observations or complications. It makes no regulatory or medical sense that a case of serious hypotension (resulting in a SAE) is described /listed as an “observation”. The applcition of their delineation between observations and complications does not appear to be discussed as relevant to the safety of the study.

While it is clear – even with this presenation – that some of the multipe AEs have been seperated out from the event descrption and coded to additional PTs, it is NOT clear that this has been done for all of the entries. Hence, there are likely more than 737 AEs that occurred in the study – but they were not all coded

Presented below are several examples of various problems with the AE capture and coding [as gleaned from Table 80]:

A: CATEGORY: Not all AEs were coded:

1.) (b) (6) (b) (6) 71 post implant
PT -> Presyncope patient became anxious when she had pain with needle insertion during refill visit. Patient held her breath,complained of lightheadness and nausea then vomited. resolved with rest. **Note: Vomiting is not typically an element of syncope& should be captured seperatly**

2.) (b) (6) (b) (6) 531 post-implant
Transient ischaemic attack -> Pt. to local ER with complaint of **severe pain/heaviness in neck/chest** through foot and transient right eye vision loss for approx. 30 min. Head CT negative. Pt. transferred to ORMC for complaint of atypical chest pain. Sub-Investigator Melisa Wilson, ARNP saw pt. in regards to study participation. Study pump interrogated and reported to be functioning appropriately. Pt. worked up with ECG, Carotid US, Echo with Bubble study and Labs (results below). Neurology saw pt. and CT testing completed. Cervical cord neurofibroma was ruled out due to history of neurofibromatosis. She was determined to have suffered "probable cardioembolic event involving the right retina and right thalamus." Pt. discharged home on (b) (6) with all symptoms resolved. **Note: It is not clear that the cardiac element of this AE was captured.**

B: CATEGORY: Questionable coding

1.) (b) (6) (b) (6) 697
Lower respiratory tract infection pt complained of chest congestion and cold symptoms **Note: a cold is not generally considered a lower respiratory infection.**

2.) (b) (6) (b) (6) 16

Diarrhea -> Pt noted recently stool turned green **Note: Diarrhea is defined as more frequent or loose stool; green stools may indicate infection but are not, necessary associated with diarrhea**

3.) (b) (6) (b) (6) 195
Thyroid neoplasm 0-1.6x1.3 cm, found on CTA head during visual disturbance workup; 1-
Thyroid nodules remained asymptomatic, but Thyroidectomy performed (b) (6)
Note the visual disturbance in this description was captured in a separate AE but the carotid arteriosclerosis was coded up to the Nervous system disorders SOC.

4.) Thrombotic events that did not seem to be classified as such:
(b) (6) (b) (6) 577
Gait Disturbance Woke up and felt unsteady with walking, veering toward the left side and fell to the floor. No loss of consciousness before, during or after the fall. Per wife appeared to have **difficulty with speech and sounded confused.** Language comprehension intact on arrival to emergency room. Emergency room B/P 110/70 and telemetry showed HR 40-50 and irregular Telemetry showed atrial flutter Per the discharge summary instructions given to the patient the last statement is: The diagnosis most consistent with your symptoms is therefore a **TIA**. TIA is not the discharge diagnosis, gait instability. **Note: this AE is internally inconsistent and was coded to the less serious of the 2 events; This was originally diagnosed as a TIA.**

C: CATEGORY: Potential misapplication of Serious criteria

1.) (b) (6) (b) (6) 247
Ankle Fracture **NOT an SAE per submission** 0-States she fell on stairs at home, went to the local emergency room and was found to have multiple fractures of the Ankle requiring surgical intervention. A temporary cast was placed on the foot. follow up surgery will be scheduled at the (b) (6). she was discharged to home; 1-as an outpatient had **open treatment of right trimalleolar ankle fracture with internal fixation**, without fixation of the posterior malleolar fragment under a femoral sciatic block.;-boot removed from ankle, AE resolved.
Note; although probably not related to the device in the study, this event could have been a secondary result of presyncope or hypotension due to the effects of the drug. The fact that it required open surgery with internal fixation of the leg suggests this is (Regulatorily) serious).

D: CATEGORY: Fragmentation of safety data by only presenting PTs and not higher MedDRA categories which could provide better insight into safety related trends.

Note: This method of presenting the safety data is misleading and unprofessional. Not only does it make analysis by the Agency more difficult, it also suggests that the Sponsor does not understand the value of a comprehensive safety data analysis. For instance in regards to Table 13 (cut & pasted below), the submission states that numerous adverse events occurred no more than three times. However, if the data in the submission had presented and analyzed AEs and ADRs at the HGLT or SOC level, a different picture would emerge; there would be more {all-cause} Infections reported. Similarly, all of the AEs “musculoskeletal pain”, “arthralgia” and “myalgia” would all be captured under the “Musculoskeletal and connective tissue disorders SOC.

Table 13: Post-Implant Adverse Events Not Related to the System with 3 or More Occurrences

Preferred Term	Number of AE's (Number of Subject, %)
Implant site pain	45 (43, 71.7 %)
Upper respiratory tract infection	27 (19, 31.7 %)
Pulmonary arterial hypertension	21 (14, 23.3 %)
Injection site reaction	17 (12, 20.0%)
Dyspnoea	17 (11, 18.3 %)
Headache	15 (12, 20.0%)
Fatigue	12 (11, 18.3 %)
Injection site pain	12 (9, 15.0%)
Dizziness	11 (10, 16.7 %)
Hypotension	11 (9, 15.0%)
Immediate post-injection reaction	11 (9, 15.0%)
Nasopharyngitis	11 (9, 15.0%)
Implant site bruising	10 (10, 16.7 %)
Nausea	10 (10, 16.7 %)
Pain in extremity	10 (10, 16.7 %)
Fluid overload	10 (6, 10.0%)
Dyspnoea exertional	9 (7, 11.7 %)
Urinary tract infection	9 (5, 8.3 %)
Flushing	8 (8, 13.3 %)
Abdominal pain	7 (7, 11.7 %)
Back pain	7 (7, 11.7 %)
Palpitations	7 (6, 10.0%)
Pneumonia	7 (6, 10.0%)
Diarrhoea	6 (6, 10.0%)
Vomiting	6 (6, 10.0%)
Oedema peripheral	6 (5, 8.3 %)
Syncope	6 (5, 8.3 %)
Sinusitis	6 (4, 6.7 %)
Anxiety	5 (4, 6.7 %)
Atrial fibrillation	5 (4, 6.7 %)
Hypokalaemia	5 (4, 6.7 %)
Musculoskeletal pain	5 (4, 6.7 %)
Adverse drug reaction	4 (4, 6.7 %)
Arthralgia	4 (4, 6.7 %)
Constipation	4 (4, 6.7 %)
Insomnia	4 (4, 6.7 %)
Pruritus	4 (4, 6.7 %)
Rash	4 (4, 6.7 %)
Right ventricular failure	4 (4, 6.7 %)
Tachycardia	4 (4, 6.7 %)
Cough	4 (3, 5.0%)
Hypoxia	4 (3, 5.0%)
Influenza	4 (3, 5.0%)
Anaemia	3 (3, 5.0%)
Bronchitis	3 (3, 5.0%)
Chest pain	3 (3, 5.0%)

Preferred Term	Number of AE's (Number of Subject, %)
Depression	3 (3, 5.0%)
Epistaxis	3 (3, 5.0%)
Fluid retention	3 (3, 5.0%)
Gastritis	3 (3, 5.0%)
Implant site swelling	3 (3, 5.0%)
Myalgia	3 (3, 5.0%)
Presyncope	3 (3, 5.0%)
Rheumatoid arthritis	3 (3, 5.0%)
Urticaria	3 (3, 5.0%)
Vertigo	3 (3, 5.0%)
Vessel puncture site pain	3 (3, 5.0%)
Abdominal discomfort	3 (2, 3.3 %)
Cardiac failure	3 (2, 3.3 %)
Tooth infection	3 (2, 3.3 %)
Injection site discomfort	3 (1, 1.7 %)
Injection site irritation	3 (1, 1.7 %)

To summarize for the AE data submitted it appears as though 1.) Not all AEs that occurred during the study were coded, 2.) There was questionable coding for some AEs 3.) There appeared to be occasional misunderstanding and misapplication of Serious criteria and 4.) In this submission, the safety data – write large- has been presented in a fragmented and manner (at the PT level) which precludes meaningful analysis.

It is also noted that for many AEs in the submission it is not clear why the same AE was designated [in one instance] a complication and [in another] was as an observation. In fact, this clinical reviewer finds this distinction unhelpful and does not accept AEs short of spurious, abnormal laboratory results as “observations” since the vast majority of AEs were, indeed, complications for the patient.

In addition, to the examples of the issues above, an inconsistent definition of the AE “Immediate post-injection reaction” appears to have been utilized in the study. This AE could be important in regards to the RIS and how the initial doses and refills should be approached using this drug delivery system. Other AEs that were coded inconsistently included incision site pain/burning/redness/swelling/ reaction, diarrhea (vs. abdominal discomfort or dehydration) and hypotension [among others].

These inconsistencies in coding might have been overlooked had the Sponsor included a thorough safety analysis with the submission. However, the Sponsor only submitted lists of AEs and pre-digested Tables of AEs (with PTs only) presented in a way that does not allow trends or pattern to be easily determined.

The Sponsor should, at the very least, re-submit the safety analysis and include:

- 1.) a numbered Table of all AEs with on verbatim term in each row of this table (NO more narratives of event description in AE tables).*
- 2.) Submit several numbered AE tables which list the AEs in decreasing order of prevalence; the Tables should include those that list AEs by SOC, HGLT and PT levels.*

The Sponsor should also present a thoughtful analysis that discusses the overall safety of the entire RIS procedure and cycle (implant, Remodulin dosing and refills). This discussion should include a separate table and subsection that discusses, analyzes and addresses all SAE in the context of the entire study. For this, all SAEs should be discussed in context of safety of device, the patient population and the trial itself.

3.) In addition to the general concerns noted above about the safety analysis, there are other specific catheter and implant -related concern; Catheters have been associated with a variety of post-insertion complications, including infection, phlebitis, thrombosis, catheter dislodgment, leakage, and occlusion. In addition, pneumothorax or hemothorax are serious events associated with some catheterization procedures. Review of the safety data in this submission raised the following specific concerns:

- a.) infections (serious and non-serious, all cause)*
- b.) thrombotic/embolic events (serious and non-serious, all cause))*
- c.) arrhythmias (serious and non-serious, all cause)*

*d.) potential under and over-dosing events (serious and non-serious, all cause)
e.) Injection site pain and injections site reactions - including refill reactions (serious and non-serious, all cause)– are these really lessened using this system?*

a.) In the submission there is not a comprehensive analysis of infections (as they relate to implantation of the entire RIS system); also, on the surface, there appears to be a large number of patients who experienced infections (including Upper respiratory tract infections in 31.7 % of patients). Please submit a thoughtful presentation of all infection –related safety data and discuss it in an analysis.

b.) The submission does not contain a thorough analysis of thrombotic /embolic events (as they relate to implantation of the entire RIS system); it does not appear as though there were many of these, however, it was noted that several thrombotic-related AEs may not have been properly captured. Review the coding of all AEs and provide a thorough presentation and analysis of all thrombo-embolic/vascular events.

c.) Given the prevalence of arrhythmias in your study population, discuss this and analyze the arrhythmias observed during the study in light of use of the RIS system in this and in the general US PAH population.

d.) Analyze and discuss potential and known under and over-dosing events that occurred during the study; discuss this as it relates to the many points of potential failure in the Redmodulin Implant system and provide a compelling argument for the utility of the system.

e.) In your submission you state that “an implantable intravascular drug delivery system does not cause infusion site pain, which is associated with subcutaneous delivery of drug experienced by up to 85% of patients. The refill of the pump can be extended from the currently frequent (at least every three days) activity to having a refill procedure occurring as infrequently as once every twelve (12) weeks (depending on patient prescription) based on the clinical study, reducing time burden.” However, it is not clear from the safety data that you provided that the pain associated with your implantable IV drug delivery system is less common or less severe than that of external IV drug delivery devices.

Catheter- comments on safety:

In the current study – Model 16042

This clinical reviewer found the presentation of catheter-related events confusing and misleading. Specifically, the fragmentation of catheter events into various causality categories obscured substantive review; for example: It is not clear – even after repeated review- why several of the “system-related” adverse events (e.g. device dislocation, device damage, venous stenosis) are not considered “catheter related” and were not captured in the analysis of the primary endpoint. Also the AE PT “device damage” is confusing at best, and misleading at worse since it is not clear that the device was itself damaged. In addition, the distinction between a ‘Sys-Rel AE’ and a “Sys-Rel Comp” is not clear. For these reasons, the reviewer has difficulty accepting the analysis of the primary endpoint (safety of the catheter).

Following each catheter implant procedure, Medtronic required implanters to complete an implant survey. Within this survey the implanter had the opportunity to give feedback on the procedure itself and the usability of all device components. This feedback is included in Table 86 on Page 388 of 465 I of the Original Clinical Studies Report.

Reviewer comment: The table in the submission provides feedback from 6 investigative sites for 34 (of the 60) patient implants performed.

The Table below was created in the course of my review of this feedback.

Issue	Number times mentioned	Number of sites
Visibility of the catheter tip and catheter body was unacceptable due to there being poor visibility of the tip. Visibility of catheter tip and catheter body under fluoroscopy: Unacceptable Specify reason: Tip not Visible	<u>11</u>	<u>7</u>
Improve tactile or audible feedback to confirm connection of catheter to pump	<u>5</u>	<u>2</u>
Catheter Length: Should be Shorter	<u>1</u>	<u>1</u>
Catheter length - should be longer	<u>4</u>	<u>3</u>
The implanter had challenges slitting the Hub of the 6208 introducer; Ability to advance catheter through introducer: Difficult , Specify reason - Tip is very soft; Other items used due to difficult bend:	<u>7</u>	<u>5</u>
Ability to push catheter through the vasculature: Difficult , Considerable difficulty passing cath via sheath. MDT peelable is too prone to kinking combined with lack of pushability of the catheter.	<u>8</u>	<u>6</u>
Ease of suturing anchor sleeve- Difficult, Specify reason: 2 anchors used with loop	<u>1</u>	<u>1</u>
From the catheter implant procedure it was commented that there needs to be easier to use ‘O’ silk .	<u>1</u>	<u>1</u>

Reviewer comment Several implanting clinicians noted that they used components of other surgical kits due to these issues: For example: “Other items used due to difficult bend: Attain Command - 6250C0005880943, Safe Sheath CSG9FCSG-90-09 (45cm), Boston Scientific/Acuity Break Away - 8F x 49cm” and “8fr SIM sheath kinked. 9fr worked”, “the “J” tip wire in the ARROW kit is ergonomically better for introducing the wire” and “there needs to be easier to use ‘O’ silk”

It is noted that the highest number of feedback comments focused on the catheter; specifically the inability to push it through the vasculature, the difficult pushing it through the introducer

and the poor visibility under fluoroscopy. These issues were noted in anywhere from 5 (50%) to 7 (70%) out of ten investigative sites for 35 (out of 60) patients.

Catheters- Model 8201 [proposed for PMA and marketing]

Reviewer comments: *From a clinical standpoint, the validity of the entire clinical study is nullified by the fact that the primary endpoint was safety related to catheter-related events – and the catheter which is being proposed for approval with the system and marketing with the pump has not been verified to adequately perform safely in a clinical scenario. The Sponsor states that the subject of this PMA (e.g. Model 8201) is to be used for marketing. It is noted that there did not appear to be any drawings or photographs of the Model 10642 to assess this or a table comparing Model 10642 with Model 8201.*

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

However, they have submitted the PMA proposing use of a completely different catheter; from a clinical standpoint, the validity of the clinical study is nullified as it relates to introduction of a newly design catheter into the system. The PMA submission states [for the first time] that: “The purpose of this clinical study was 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). The Sponsor concludes that “ The DelIVery for Pulmonary Arterial Hypertension (PAH) Clinical Study demonstrated the Implantable Intravascular Catheter is 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 Remodulin® Implantable System.”

Reviewer comment: *This is not a logical supposition since the entire point of the study was to test the new catheter with this system. The catheter which is being proposed for approval [Model 8201] with the system and marketing with the pump has not been clinically tested at all from what we can discern. The Sponsor did not clinically assess the final product.*

Of note, The Sponsor worked collaboratively with the FDA to develop objective performance criteria (OPC) based on the following events for external central venous catheters in the literature:

- 1. Catheter Disconnect*
- 2. Catheter Dislocation/Dislodgment*
- 3. Catheter Occlusion*
- 4. Catheter Breakage*
- 5. Bloodstream Infection/ Sepsis*
- 6. Site Infection*

7. *Pneumothorax*
8. *Venous phlebitis and/or thrombosis*
9. *Subcutaneous Catheter Leakage*

Given the new elements being introduced in Catheter Model 8201, these performance criteria would need to be re-studied and re-evaluated as there has been more than one change to the catheter and both changes were based on ADRs; however, the changes to the catheter were never tested clinically since the Sponsor stopped the study when they believed they reached their “catheter-safety: endpoint.

The stated addition of a two longer catheter sizes and an additional 2-piece anchor sleeve on the Model 8201 raises concerns about both ease of use and the potential thrombogenicity. There will also be a new suture-less s connector used with both the Model 8201 and the Model 16042 that has not previously been studied clinically since it was approved only in 2013 (almost 7 months after the last patient in this study was enrolled).

As is widely known and re-iterated in the RIS labeling “Catheters should not be forced through vasculature; nor should they be kinked, stretched or severely bent”. There is evidence that the study investigators had difficulty advancing the 80 cm catheter. There is no evidence as to whether longer catheters will or will not be more difficult to advance or result in more kinking and stretching of the catheter (which could lead to ADRS and AEs) Applying force may injure the patient’s vasculature or heart.

There has been no use of the various sized catheters; 80 cm was used on all patients in the PiVoT study, now the Sponsor is proposing two more lengths. Selecting a catheter that is too short may result in dislodgement of the catheter from the vasculature or may cause patient discomfort because of insufficient strain relief. Selecting a catheter that is too long may result in difficulty wrapping the excess length and securing it under the pump. Selecting a catheter that is too long and unwieldy could also, feasibly lead to additional complications such as pneumothorax. The clinical study performed under this PMA does not address these issues.

ANCHOR:

Adverse Events Related to Anchoring at the Venotomy Site:

The submission recounts those facts that, on March 13, 2012, Medtronic temporarily suspended enrollments and implants in the clinical study to investigate the causes of three catheter dislocations that had occurred in two subjects of the first 21 implants or catheter replacements.

These were classified as related to the catheter. In all three cases, the catheter retracted outside of the vasculature. All three dislodged catheters were revised by either replacing their entire system or only the catheter.

An IDE-Supplement (G100017/S018) was submitted to FDA on March 14, 2012 notifying FDA of a UADE due to a higher than expected rate of catheter dislodgments/dislocations. Medtronic also notified FDA of Medtronic’s decision to temporarily suspend enrollments and implants in the DelIVery for PAH study.

Medtronic determined the cause of the catheter dislocations were due to the sutures on the anchoring sleeve not achieving and maintaining adequate compressive force on the catheter.

To mitigate the risk of catheter dislocations, the implanting clinicians were trained on new anchoring instructions which consisted of tying anchoring sleeve sutures tight enough so that indents could be visualized on the catheter using fluoroscopy. The Sponsor claims that with the updated procedure, 46 additional implants or catheter change-outs were completed without any dislodgments being reported (0%). However, the Sponsor proposes to change the anchor sleeve on the catheter to a new 2-piece design which has not been clinically tested.

Primary Objective: The primary objective was designed to demonstrate that the Model 10642 Implantable Intravascular Catheter was safe when used with the Medtronic SynchroMed II Implantable Infusion System to deliver Remodulin Injection.

Hypothesis

HO: Rate of catheter-related complications ≥ 2.5 per 1000 patient days

HA: Rate of catheter-related complications < 2.5 per 1000 patient days

Per the Sponsor’s assessment, they claim that “if the one-sided upper 97.5% confidence bound of the rate of catheter-related complications was less than 2.5 per 1000 patient days, then it could be demonstrated that the Model 10642 Implantable Intravascular Catheter was safe. 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. This occurred on June 21, 2013. Refer to Table 1 [cut & pasted from the submission] for a summary of the primary objective results as of June 21, 2013.”

A successful implant is defined as the SynchroMed II Implantable Infusion System with the Implantable Intravascular Catheter being implanted and priming bolus completed.

Table 1 Summary of Primary Objective Results at the Pre-specified Analysis Point

Objective and Performance Criteria	Results
Catheter-Related Complications:	Catheter-Related Complications: 6
To demonstrate that the Model 10642 Implantable Intravascular Catheter is safe when used with the Medtronic SynchroMed II Implantable Infusion System to deliver Remodulin.	Patient Days: 22,013
Performance Goal: rate per 1000 days < 2.5	Catheter-Related Complications per 1000 days: 0.27
	One-sided upper 97.5% confidence bound: 0.59
	P-value: < 0.0001
	Objective Met

The Sponsor then states that “due to the length of time between June 21, 2013 and the submission of the PMA report, an update of the data in this clinical report is included. Therefore, all other data in this report is as of July 25, 2014. Table 2, includes an update of the primary objective data. The p-value is not presented again because the pre-specified analysis plan called for one look at the p-value (at 22,000 days).” [Table 2 is pasted from the submission]

Table 2 Updated Summary of Primary Objective Results

Objective and Performance Criteria	Results
Catheter-Related Complications:	Catheter-Related Complications: 7
To demonstrate that the Model 10642 Implantable Intravascular Catheter is safe when used with the Medtronic SynchroMed II Implantable Infusion System to deliver Remodulin.	Patient Days: 44,085
Performance Goal: rate per 1000 days < 2.5	Catheter-Related Complications per 1000 days: 0.16
	One-sided upper 97.5% confidence bound: 0.33

Pre-specified Analysis Methods: The endpoint of this objective was catheter-related complications per 1000 patient days. The number of catheter-related complications per 1000 patient days was estimated using all subjects with an implant attempt. A one-sample exact test for the Poisson rate was used to obtain the 97.5% one-sided upper confidence bound of the catheter-related complications.

Table 34 Primary Objective: Catheter-Related Complications at the Pre-specified Analysis Point

Performance Goal	Patient Days	Catheter-related Complications	Catheter-related Complications Per 1000 Days	One-sided upper 97.5% confidence bound	P-value
Rate per 1000 days < 2.5	22,013	6	0.27	0.59	<0.0001

The remainder of this report (other than the p value of the primary endpoint) includes data through July 24, 2014.

Table 35 Primary Objective: Catheter-Related Complications - Updated

Performance Goal	Patient Days	Catheter-related Complications	Catheter-related Complications Per 1000 Days	One-sided upper 97.5% confidence bound
Rate per 1000 days < 2.5	44,085	7	0.16	0.33

The Sponsor states that “comparing the results with this system to the other primary treatment for these patients, the central venous catheter system, published data in the PAH population suggests a rate of central venous catheter (CVC) systemic infections for bloodstream infections (BSI) at 0.4336 to 1.1337 per 1000 patient days and site infections at 0.2638 to 0.8739 per 1000 patient days while complications from catheter thrombosis, mechanical dysfunction, and catheter dislocation in the general CVC population contribute another 0.3640,41-0.5142 events per 1000 patient days. This leads to a combined rate of catheter-related complications of between 1.05 and 2.51 per 1000 patient days in the CVC system. In literature published after development of the protocol, a BSI rate of 0.3643 per 1000 patient days for patients treated with IV treprostinil was

reported, which would lead to an updated combined rate of catheter-related complications of between 0.98 and 2.51 per 1000 patient days in the CVC system. To best match the literature, any pneumothorax complication was counted as a catheter-related complication for this endpoint.”

Reviewer comment: For numerous reasons elucidated throughout this review, I cannot accept the data or analysis that went into formulating this endpoint or its conclusion.

Efficacy:

During the development of this protocol, the Sponsor met with representatives from the FDA’s CDRH numerous times. During this period, it was decided that efficacy could not and should not be assessed as an endpoint in this clinical trial. This excerpt from a consulting review memo by Dr. Deborah Shure, MD (July 9, 2010), sums up the result of this decision most succinctly. Dr. Shure states that “I agree with the sponsor, however, that effectiveness of the drug cannot be reasonably tested in this patient population in a single-arm study. Pulmonary arterial hypertension is progressive disease. The course may be variable within individuals and the drug dosage will be adjusted according to symptoms and functional status during the course of the study. Furthermore, patients will be in the study for varying lengths of time. Such a design does not permit assessment of drug effectiveness. I believe that drug effectiveness has been established through the drug clearance process. If the pump and catheter perform as specified in preclinical testing, the issue of importance is clinical safety in this patient population.”

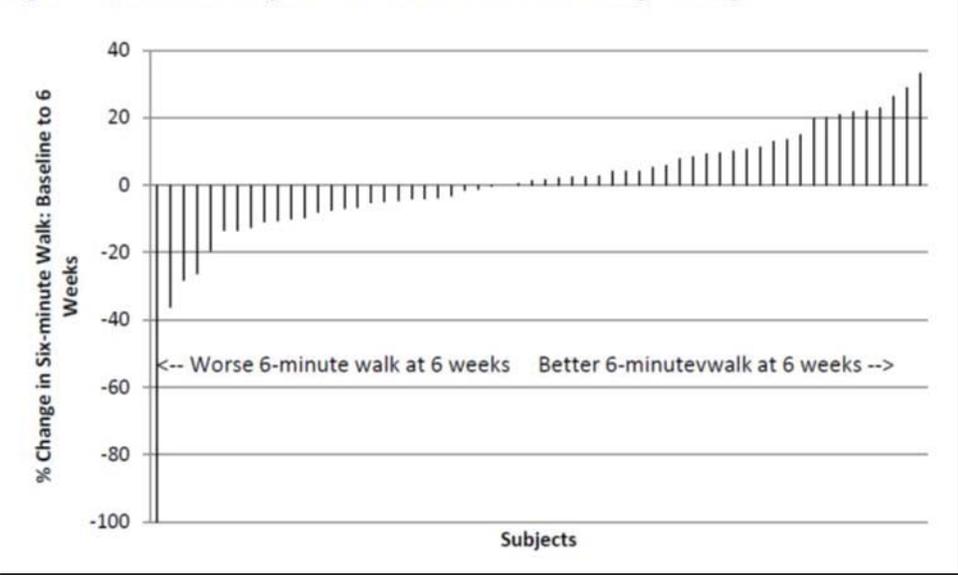
Dr Shure to stated that a clinical study is still indicated to assess safety because the catheter has a novel sleeve mechanism that has not been tested in humans and concerns related to thrombosis and infection in particular cannot adequately be assessed in an animal model. I am not aware of an animal model that would adequately mimic this complex patient population in order to adequately assess safety.”

Despite this, the Sponsor did make efforts to gauge efficacy in the study. A few of the ancillary, efficacy-related endpoint are discussed here.

Six minute walk:

The submission states that “percent change in six-minute walk for each of the 58 subjects with paired data at baseline and six weeks is presented. It is ordered from the subject with the largest percent decrease in distance to the subject with the highest percent increase. Of the 58 subjects, 32 (55%) stayed the same or had an increase in their six-minute walk distance and 26 (45%) had a decrease in their six-minute walk distance”.

Figure 5 Individual Subjects' Six-minute Walk Percentage Changes



In addition to 6 weeks post-implant, the six-minute walk was collected at the 3, 6, and 12-month visits. The Sponsor states that “The measured distance walked was not expected to change significantly due to the fact that the treatment therapy being provided in this study is the same therapy received at baseline; only the drug delivery method of using an internal versus external drug delivery system has changed.

Reviewer comments: *The Sponsor did not expect the six minute walk time to improve but what have they to say about the fact that 45% of patients -almost half- had worse performance after 6 weeks?*

The Sponsor also attempted to conduct a quality of life assessment during the clinical study: The summarized results are shown below:

Table 41 CAMPHOR Baseline to Six Months Results

	Symptom Scale	Activity Scale	QoL Scale
Mean Score Change ± S.D.	-0.37 ± 3.51	1.03 ± 3.10	-0.51 ± 3.07
95% Confidence Interval	(-1.30, 0.56)	(0.20, 1.85)	(-1.32, 0.30)
<u>Change</u>			
Better	19 (33%)	10 (18%)	18 (32%)
No Change	24 (42%)	26 (46%)	29 (51%)
Worse	14 (25%)	21 (37%)	10 (18%)

Per the submission “ At six weeks post-implant, according to the FACIT-TS-G survey, subjects were satisfied with the therapy with a mean treatment satisfaction score of 94.7 (out of 100) and a mean recommendation score of 98.3. For the question “How do you rate this treatment overall?”, at six weeks and at six months all subjects (with no missing data) reported good, very

good, or excellent. Also, at 6 months, 53% felt the effectiveness of the treatment was better than expected. Overall, there was little change in quality of life measured by these instruments over 6 months, which is not unexpected given the progressiveness of PAH.”

Reviewer comment: *The Sponsor has selectively extracted data points that were more in their favor in regards to how this implantable system impacts quality of life {QoL}. However, in the table above it is clear that the majority of patients in the study felt either no change in their overall QoL or a worse QoL. Thus, when one looks at the data overall, along with factors related to safety issues associated with the implant procedure as well as potentially inaccurate Remodulin doing (based off of the flow rate accuracy and the number systemic AEs captured in this study), it is not clear that the risk-benefit profile of this system is beneficial for patients.*

Discussion on Plasma Treprostinil (collected during the study):

Description of Study Specific Procedures - Blood Sample Collection for Treprostinil:

At baseline and 1 week follow-up: A blood sample was be collected for analysis of plasma treprostinil levels. The 1 week follow up sample was drawn at the same time of day (within +/- two hours) as the baseline sample due to diurnal variations in plasma treprostinil levels. At suspected catheter occlusion: A blood sample was collected for analysis of plasma treprostinil levels if a subject had a suspected catheter occlusion adverse event in order to assist in adverse event adjudication.

Table 67 Plasma Treprostinil Levels (K2 and K3 Samples)

Time	
Baseline	
n recorded	59
Mean ± Standard Deviation (ng/mL)	10.9 ± 6.1
Median (ng/mL)	9.7
Range (ng/mL)	1.5 - 35.1
1 week	
n recorded	58
Mean ± Standard Deviation (ng/mL)	10.5 ± 5.6
Median (ng/mL)	10.2
Range (ng/mL)	2.5 - 31.4
Percentage Change at 1 Week	
n recorded	58
Mean ± Standard Deviation	2.3% ± 41.0%
95% Confidence interval	(-8.5%, 13.0%)
Median	-1.7%
Range	-60.5% - 235.5%

Plasma treprostinil values that used the K3EDTA anticoagulant to collect the data show a slight

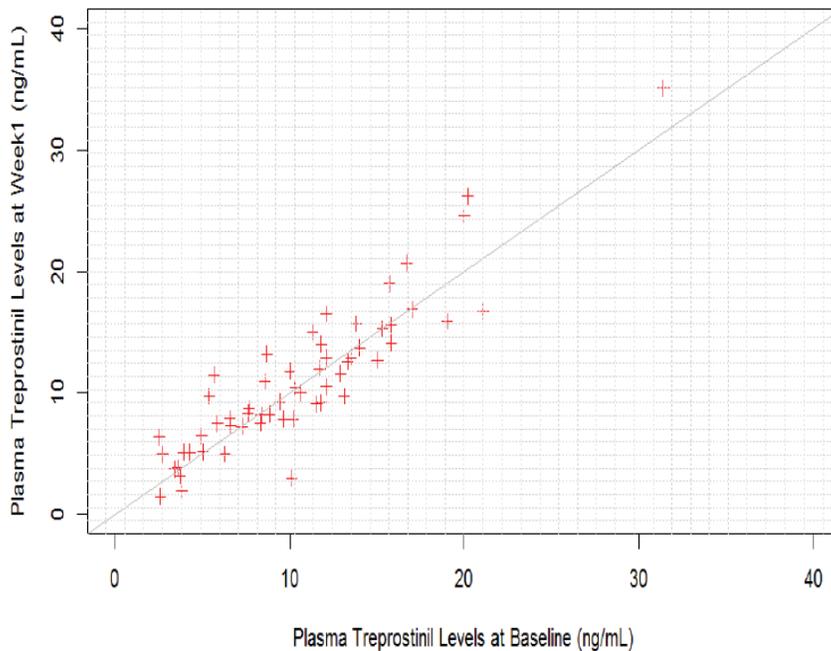
increase by an average of 2.4% (Table 67 and Table 68).

Table 68 Plasma Treprostinil Levels (K3 samples only)

Time	
Baseline	
n recorded	57
Mean ± Standard Deviation (ng/mL)	10.8 ± 6.2
Median (ng/mL)	9.7
Range (ng/mL)	1.5 - 35.1
1 week	
n recorded	58
Mean ± Standard Deviation (ng/mL)	10.5 ± 5.6
Median (ng/mL)	10.2
Range (ng/mL)	2.5 - 31.4
Percentage Change at 1 Week	
n recorded	56
Mean ± Standard Deviation	2.4% ± 41.6%
95% Confidence interval	(-8.7%, 13.5%)
Median	-1.7%
Range	-60.5% - 235.5%

The Sponsor states that Figure 24 shows that plasma treprostinil concentrations via external system and internal implantable PIVoT system did not vary significantly. Externally delivered and internally delivered treprostinil have therapeutic equivalence.

Figure 24 Plasma Treprostinil Levels (K2 and K3 Samples)



Reviewer comments: *This reviewer must defer evaluation of treprostinil levels to CDER as this reviewer does not have the background for determining if this range of fluctuation is acceptable (though Sponsor points out that this is acceptable in a chronic implant pump)*

Pump accuracy : The Sponsor provides the following Discussion on Pump Fluid Delivery Accuracy. They explain “There were 1109 refills with 61 pumps used during refill with data reported to calculate refill accuracy. The mean accuracy ratio per pump was 0.93 (with a standard deviation of ± 0.04). The percentage of refills with acceptable refill accuracy was 99.9%. This was shown by plotting the accuracy ratio of all refills on the flow rate accuracy chart in Figure 21. One refill was outside of the pump refill accuracy range. No AEs were reported in conjunction with this event.”

Device Malfunctions: Per the submission, a “device malfunction was defined as a SynchroMed II Remodulin Implantable System Programmable Pump (Model 8637), Implantable Intravascular Catheter (with sutureless connector) (investigational, Model 10642), and/or the N’Vision Clinician Programmer (Model 8840) with application software (Model 8870) failure, malfunction or function not according to design intent which did not result in an adverse event.”. According to the PMA, there were only two device malfunctions in the study; however, it is not clear why the under and over-dosing issues were not reported as device malfunctions if they did not result in AEs.

Reviewer comment: *The calculation of the accuracy of the pump appears acceptable on its surface; however, it is difficult to ascertain how this aspect of device performance impacts the thermal function and dose accuracy issues. It would be helpful if the Sponsor provided an analysis of pump accuracy that also took flow rate, “device malfunction” (including under-dosing that has been recorded) and the spectrum of adverse events associated with under and over-dosing of Remodulin into account. Without this type of integrated clinical evaluation, the “pump accuracy” data is relatively meaningless.*

System modifications: On page 407 of the pdf of the Original Clinical study report presents a table that shows the seven system modifications and five deaths as well as the device disposition of each returned product. However, there is not description as to why the seven systems were “modified”. ***Reviewer comment:*** *Please explain why and how seven systems were “modified” in your response along with a site breakdown indicating at which sites the modifications occurred. It is noted that there were several modifications listed under just one patient ID number. Please explain the sequence of events that led to this and describe any sequelae.*

Additional, Ongoing ISSUES:

1.) Design Change for Model 8637 SynchroMed II for RIS made after Design Verification Test (DVT) Builds

The submission describes a design change to the market approved Model 8637 SynchroMed II infusion system that is currently under review by FDA (P860004/S217, submitted 31-Oct-2014).

Supporting documents for this supplement are not provided under this PMA. These documents are available upon request and address, primarily the SynchroMed II Gear Design Enhancement. The gear wheel 3 material is currently a Copper-Nickel-Zinc Alloy (ARCAP) and this submission requests to change this component to a stainless steel material (NTK-F2) to increase the robustness of this gear to corrosion while maintaining wear resistance. The Remodulin Implantable System premarket approval (PMA) application includes the new design with the submitted gear wheel 3 material change. After FDA approval of the gear material change, and subsequent implementation, the risk of corrosion-related failure in the SMII pump will be further reduced for Remodulin use. Qualification, Verification or Validation of the Change Medtronic determined the material loss seen on gear wheel 3 is the result of the combined effect of corrosion and wear due to environmental and gear train stresses.

An analysis by the Sponsor regarding pump corrosion associated with Remodulin, its active ingredient and metacresol was conducted and concluded that there is no increased risk of corrosion in the SynchroMed II pump for Remodulin infusion. They claim that the pending FDA approval and subsequent implementation of the gear wheel 3 material change shall further reduce the risk of corrosion-related failure in the SynchroMed II pump; Corrosion rates on the same order of magnitude were observed in indicated drugs and non-indicated drugs. They state further that “his implies that the active pharmaceutical ingredients (API) do not have observable effect on the corrosion rates, but the excipients (e.g. saline based formulation) in which the drug is formulated in are the main contributors. Other than the API and Metacresol, Remodulin formulation uses similar excipients as other drug formulations, mainly sodium chlorides. Chlorides are known aggressive species that cause corrosion on many metal and alloys, ARCAP included. Therefore, ARCAP gear wheel 3 is expected to have comparable corrosion rate in the SMII pump infused with Remodulin as compared to other drugs with extended known use history in the SMII pump”.

Reviewer comment: It is not clear to this reviewer how the FDA can approve this rather complex device and system when it is so reliant on a set of parts & mechanism that has not been demonstrated to be robust. As a clinician, it does not make sense to approve this prior to full testing, validation and approval of the design changes (in the other application[s]) as this could negatively impact the patient’s QoL if the gears wore out prematurely and the system had to be changed more frequently or discontinued. Clinically this is unsettling; the stated life span of the pump is currently between 2- 7 years. If the pumps lasts less than 2 years, then this would likely negatively impact the risk-benefit for the PAH patient.

2.) Chilling and corrosion: The Medtronic response to the chilling and corrosion issue concludes that “the time duration of thermal cycling of the SynchroMed II pump due to chilled drug is insignificant compared to duration of thermal cycling due to normal use conditions of an implanted pump. The temperature range of thermal excursions of the SynchroMed II pump due to chilled drug is close to the range of temperatures that can be seen in an implanted device. Therefore, chilled drug does not cause significant acceleration of SynchroMed II pump corrosion due to condensation from temperature excursions due to chilled drug.” They go on to claim that, due to this, “The introduction of chilled drug would not be expected to increase motor corrosion for the following reasons:

- The SynchroMed motor is designed to be at up to 100% relative humidity with condensing water during use conditions, which include variations of temperature.
- Temperature excursions due to chilled drug are close to the range of temperature excursions expected from normal-use conditions.
- The time duration of thermal cycling of the SynchroMed II pump due to chilled drug is insignificant compared to duration of thermal cycling due to normal use conditions of an implanted pump”

Reviewer comment: *The response to this issue appears to make sense; however, clinically, the Sponsor has not really provided a comprehensive review of exactly how and to what degree the use of chilled drug impacts adverse effects associated with the RIS system. Therefore, I defer to the engineering Reviewer to determine if their analyses and response is acceptable.*

3.) Miscellaneous items:

Reviewer comments: *The Procedures for and Results of Patency testing is part of this PMA submission. It is not clear if and how the patency testing procedures were validated, nor if the three tests performed are of clinical significance. All three tested as patent. It is noted that the syringe method of testing patency (as described in the submission) appears to be extremely difficult, if not impossible for a clinician to perform precisely and consistently.*

Reviewer comments: Study deviations: *100 study deviations were reported during the study; these are summarized as follows - 7 pumps not implanted per protocol, 7 out of 60 is a considerable number describe why and potential impact .*

It is observed, by reading the study deviation descriptions, that many (at least 21) refill procedures in the study were completed outside of the time period states in the protocol; please provide analysis of the refills in the study in which you characterize and compare the refills done both within and outside of the stated timelines. This analysis should characterize the refills outside and within the appropriate windows and correlate them to both adverse effects, six minute walk time, CAMPHOR scores and other relevant attributes that were measured in this study.

It is noted that presentation of the study deviations does not make it clear whether these deviations occurred more in one site or whether more than one study deviation was attributed to one patient. The Sponsor should provide a presentation of the study deviations by study site and by patient (e.g. How many patients were involved [i.e. is the same patient who was not consented the same one who also did not meet the exclusion criteria)? Currently it is only presented by type of deviation.

Additionally, There are at least 6 instances where the system was implanted on wrong side; the Sponsor should provide a discussion for this (which addresses the possibility that implant instructions may change based on the fact that 1 out of every 10 implants was implanted on the “wrong” side). This should be clarified in the labeling?

IV. Recommendations & Proposed Responses to Sponsor

For numerous reason elucidated throughout this review, I cannot accept the data or analysis that went into formulating the endpoint analysis for this PMA or its conclusions.

Recommendation for the Remodulin Implantable System (Model 8201 catheter):

Do not approve; the agreed-upon primary endpoint of this clinical study was to assess safety of the new Model 10642 catheter (along with a comprehensive risk-benefit analysis and assessment of the devices ability to accurately deliver the proper amount of drug). The newer Model 8201 catheter has multiple additional new components (different lengths, a new suture-less connector and a new 2-piced anchor) which can only be tested clinically and which were not tested in this study. Furthermore, the fragmented and poorly captured /analyzed safety data in this submission unduly hindered independent and comprehensive safety analyses (of the primary endpoint and the study overall) by the Agency.

Recommendation for the Remodulin Implantable System (Model 10642 catheter):

Do not approve; the agreed-upon primary endpoint of this clinical study was to assess safety of the Model 16042 catheter (along with a comprehensive risk-benefit analysis and assessment of the devices ability to accurately deliver the proper amount of drug). The fragmented and poorly captured / analyzed safety data in this submission impeded independent and comprehensive safety analyses (of the primary endpoint and the study overall) by the Agency. In addition, when one looks at the risk-benefit profile as a whole and factors in issues associated with the device itself, the implant procedure and the potentially inaccurate Remodulin dosing (based on the flow rate accuracy and the systemic AEs captured in this study), it is not clear that the risk-benefit profile of this system is beneficial for patients.

Deficiencies & Comments:

1.) Model 8201 Catheter: You should recall that we worked collaboratively to develop objective performance criteria (OPC) based on the following events for external central venous catheters in the literature:

1. Catheter Disconnect
2. Catheter Dislocation/Dislodgment
3. Catheter Occlusion
4. Catheter Breakage
5. Bloodstream Infection/ Sepsis
6. Site Infection
7. Pneumothorax
8. Venous phlebitis and/or thrombosis
9. Subcutaneous Catheter Leakage

In the Original Clinical Studies Report submitted with the PMA application, there is a subsection entitled “Document Change History Clinical Investigation Plan DelIVery” (on page 1 of 39). Nowhere in this document is there mention that the you intended to use and/or market a catheter different than the Model 10642 noted in version 5 of the Clinical Study protocol dated February

2, 2011. However, at several other places in the current PMA submission, you re-state the primary goal of the study as follows: “The Remodulin Implantable System is a programmable, implantable drug delivery system for chronic intravenous infusion of Remodulin in patients with Pulmonary Arterial Hypertension (PAH). The Remodulin Implantable System includes Model 8637 SynchroMed II Programmable Pump for RIS (CFNs 8637P20 and 8637P40); Model 8201 Implantable Intravascular Catheter, Model 8840 N’Vision Clinician Programmer, and Model 8870 Application Card. “

The new elements being introduced in Catheter Model 8201 could very likely effect each of these performance criteria and, thus, this Model would need to be re-studied and re-evaluated. Indeed, both of the major changes to the Model 8201 catheter were based on ADRs.

The stated addition of a two longer catheter sizes and an additional 2-piece anchor sleeve on the Model 8201 raises concerns about both ease of use and the potential for thrombogenicity. The new suture-less connector being proposed for use with both the Model 8201 and the Model 16042 also has not been studied clinically since it was approved only in 2013 (almost 7 months after the last patient in this study was enrolled).

The Model 8201 catheter was not studied in the clinical study presented for evaluation in this PMA and there is no data to suggest that it has ever been studied clinically. As this is a chronically implanted device which has proposes to introduce three new untested elements (e.g. a 2-pice anchor sleeve, two additional catheter lengths, and a new suture-less connector), this is not acceptable. If you wish to purse development and use of the Model 8201 catheter you will need to provide justification and propose an adequate clinical study to clinically test the new catheter. Additional point to consider:

- It is noted that the highest number of feedback comments from implanting investigators focused on the catheter; specifically the inability to push it through the vasculature, the difficult pushing it through the introducer and the poor visibility under fluoroscopy. These issues were noted in anywhere from 5 (50%) to 7 (70%) out of ten investigative sites for 35 (out of 60) patients. You will need to address this in the response to our concerns about the catheter.

[Note to The Lead Reviewer; you should ensure that if the Sponsor decides to pursue PMA approval with the Model 10642 catheter that was studied (after resolving all of the deficiencies), then the Sponsor should be explicitly informed that they will need to submit any modifications of the catheter to the Agency for review and additional testing (including clinical studies) may be required before it could be marketed.

2.) It is noted that the Agency has yet to receive your response to our request (G100017/R003) that you conduct and submit a more thorough safety analysis regarding the pump performance issue wherein you have asserted that gas permeation from Remodulin is resulting in under dosing, the rate of under dosing stabilizes at an accuracy ratio of 0.8 and no clinically significant adverse events have resulted due to this issues.

The below is copied and pasted from the Agency letter sent to the Sponsor on Jan 22, 2015:

The Food and Drug Administration (FDA) has reviewed the interim progress report to your Investigational Device Exemption (IDE) application and has determined that additional information is required. Please address the following questions and concerns:

The safety analysis (e.g. “Potential PAH AEs”) you have provided is cursory and insufficient to adequately evaluate whether this issue may have impacted patient safety or efficacy of the treatment. According to Table 1: Potential PAH AEs per Month throughout Study which was submitted in your response, there were 161 AEs in the study. Please provide a more detailed analysis of AEs & SAEs submitted for the duration of the trial (including prior to noticing that there was a device issue).

For these analyses – at a minimum, please provide:

- a. separate summary tables of AEs (using Medical Dictionary for Regulatory Activities [MedDRA- indicate version]) in order of decreasing frequency by System Organ Class (SOC), High Level Group Term (HLGT), and Preferred Term (PT);
- b. a table of AEs (using PT) broken down by investigative site;
- c. a table listing all reported SAEs (by both HLGT and PT);
- d. all of the raw safety data (e.g. AE verbatim terms the PT term to which they were coded as well as SAE reporting forms with narratives) for all AEs in the study;
- e. a table which lists AEs (by PT) and indicates which of these were determined by the treating Investigator to be “Related”, “Probably related”, “Possibly related” and of “Unknown” relationship to the device/treatment.

Also present AE data which will indicate when (during the trial and the subject’s therapy) the AE occurred relative to the pump being implanted and also refilled. If there were multiple events experienced by one patient, please present this data separately (in table form) in the response.

Finally, include the company’s critical, medical analyses of the requested data in a Clinical Safety Summary Report. Please note that in addition to what has been requested above, you may include up to 30 pages of additional data to discuss/explain the potential patient safety impact of this device issue. [See full letter sent in Appendix E]

3.) Adverse event reporting and Safety Analysis: Throughout the IDE and the pre-PMA submission processes we have reiterated the fact that ALL system complications will be considered in the device evaluation process. In addition, risk-benefit will be assessed looking at the totality of the data – not just the pre-specified catheter-related events. Noted again here is the fact that this study was designed around the Model 16042 catheter (which utilized a one-piece anchor sleeve and two sutureless connector components for this trial). These comments are provided in this context.

Presentation and Quality of Clinical Safety Data: The presentation of safety data lacks transparency; presentation of the safety data in bundles of separate categories or in tables [by assumed causality] with confusing and mixed categories is sub-optimal for analysis. The quality of AE capture and coding in this PMA submission is unacceptable; it is difficult to navigate and it is difficult to determine if all AEs have truly been captured in order to validate the coding and safety analysis. For example, in Table 80 which lists of “all 737 AEs in the study” [presented by the Sponsor on page 24-184 of Volume 24 of the Original Clinical study report], the entire narratives are captured in the description box (instead of just a single verbatim term). Also, this extremely long table is not numbered so there is no way to ascertain the number of rows in the table short of manually counting them. In addition, the information in Table 80 is lumped together in a way that is nonsensical from a safety standpoint. The application of the Sponsor’s delineation between observations and complications does not appear to be discussed as relevant to the safety of the study.

While it is clear that some of the multiple AEs have been separated out from the full event description and coded to additional PTs, it is NOT clear that this has been done for all of the entries. Hence, there are likely more than 737 AEs that occurred in the study – but they were not all coded. To summarize: it appears as though 1.) Not all AEs that occurred during the study were coded, 2.) There was questionable coding for some AEs and 3.) There appeared to be occasional misunderstanding and misapplication of Serious criteria.

In addition, to the examples of the issues above, an inconsistent definition of the AE “Immediate post-injection reaction” appears to have been utilized in the study. This AE could be important in regards to the RIS and how the initial doses and refills should be approached using this drug delivery system. Other AEs that were coded inconsistently included incision site pain/burning/redness/swelling/ reaction, diarrhea (vs. abdominal discomfort or dehydration) and hypotension [among others].

These inconsistencies in coding might have been overlooked had the Sponsor included a thorough safety analysis with the submission. However, they only submitted lists of AEs and pre-digested Tables of AEs (with PTs only) presented in a way that does not allow trends or pattern to be easily determined. .

The Sponsor should, at the very least, re-submit the safety analysis and include:

- a.) A numbered Table of all AEs with one verbatim term in each row of this table (NO more narratives of event description in AE tables).
- b.) Submit several numbered AE tables (with one verbatim term in each row) which list the AEs in decreasing order of prevalence; these Tables should also include list AEs by SOC, HGLT and PT levels.

You should also present a thoughtful analysis that discusses the overall safety of the entire RIS procedure and cycle (implant, Remodulin dosing and refills). This discussion should include a separate table and subsection that discusses, analyzes and addresses all SAEs in the context of the entire study. For this, all SAEs should be discussed in context of safety of device, the patient population and the trial itself.

c.) In addition to the general concerns noted above about the safety analysis, there are other specific catheter and implant -related concerns; Catheters have been associated with a variety of post-insertion complications, including infection, phlebitis, thrombosis, catheter dislodgment, leakage, and occlusion. In addition, pneumothorax or hemothorax are serious events associated with some catheterization procedures. Review of the safety data in this submission raised the following specific concerns:

- 1.1. infections (serious and non-serious, all cause)
- 1.2. thrombotic/embolic events (serious and non-serious, all cause))
- 1.3. arrhythmias (serious and non-serious, all cause)
- 1.4. potential under and over-dosing events (serious and non-serious, all cause)
- 1.5. Injection site pain and injections site reactions - including refill reactions (serious and non-serious, all cause)– are these really lessened using this system?
 - In the submission there is not a comprehensive analysis of infections (as they relate to implantation of the entire RIS system); also, on the surface, there appears to be a large number of patients who experienced infections (including Upper respiratory tract infections in 31.7 % of patients). **Please submit a thoughtful analysis and presentation of all infection –related safety data and discuss it in context of the device, the patient population and the entire RIS system.**
 - The submission does not contain a thorough analysis of thrombotic /embolic events (as they relate to implantation of the entire RIS system); it does not appear as though there were many of these, however, it was noted that several thrombotic-related AEs may not have been properly captured. **Review the coding of all AEs and provide a thorough presentation, analysis, and discussion of all thrombo-embolic/vascular events.**
 - **Given the prevalence of arrhythmias in your study population, discuss this and analyze the arrhythmias observed during the study in light of use of the RIS system in this and in the general U.S. PAH population.**
 - **Analyze and discuss potential and known under and over-dosing events that occurred during the study; discuss this as it relates to the many points of potential failure in the Redmodulin Implant system and provide a compelling argument for the utility of the system.**
 - In your submission you state that “an implantable intravascular drug delivery system does not cause infusion site pain, which is associated with subcutaneous delivery of drug experienced by up to 85% of patients. The refill of the pump can be extended from the currently frequent (at least every three days) activity to having a refill procedure occurring as infrequently as once every twelve (12) weeks (depending on patient prescription) based on the clinical study, reducing time burden.” However, it is not clear from the safety data that you provided that the pain associated with your implantable IV drug delivery system is less common

or less severe than that of external IV drug delivery devices. **Provide a safety data and a comprehensive discussion to make your case.**

Additional issues with the safety data and reporting:

- It is noted that nearly one-third of all AEs in the clinical study for this PMA's two-year long clinical study were adjudicated on a single day (November 26, 2012). What were the quality control or quality assurance processes in place to ensure that time constraints and the (non-voting) presence of the Primary Study PI did not adversely impact AE review and adjudication?
- The 22 pre-implant AEs were reviewed. All of them appear to be obviously unrelated to any RIS component or procedure. However, a few of these AEs beg questions about the conduct of the trial. Specifically, was the patient who had Klebsiella bacteremia allowed to proceed with receiving the implant? Also did the patient who tested positive for urine leukocyte esterase go on to test negative for this before proceeding with the implant procedure? These are two instances which could set a patient up for an AE or implant failure due to infection.
- The definition of unavoidable events is acceptable; however, in presenting the actual PMA data, no timeframes are given for these events to ascertain whether they met the defined requirements. The AEs were also not discussed in the context of the entire implant procedure and how this impacts the risk-benefit of the Remodulin Implantable System.
- This presentation of catheter-related events was confusing and seemed also to be somewhat misleading. Specifically, the fragmentation of catheter events into various causality categories obscured substantive review; for example: It is not completely clear why several of the "system-related" adverse events (e.g. device dislocation, device damage, venous stenosis) are not considered "catheter related" and were not captured or discussed in the analysis of the primary endpoint. Also the AE PT "device damage" is confusing at best, and misleading at worst since it is not clear that the device was itself damaged. In addition, the distinction between a "Sys-Rel AE" and a "Sys-Rel Comp" is not clear.

4.) Efficacy: In regards to your efficacy analyses, it is clear that the majority of patients in the study felt either no change in their overall QoL or a worse QoL. Thus, when one looks at the data overall, along with factors related to safety issues associated with the implant procedure as well as potentially inaccurate Remodulin dosing (based off of the flow rate accuracy and the number systemic AEs captured in this study), it is not clear that the risk-benefit profile of this system is beneficial for patients.

5.) 20 ml pump: The submission states that UTC will submit an NDA supplement to add RIS to the Remodulin labeling for the undiluted 2.5 mg/mL, 5.0 mg/mL, and 10.0 mg/mL concentrations. However, it is noted that only one patient received the Model 8637-20 pump (20 ml pump) while the rest were implanted with the 40 mL. It is not clear that this will be considered adequate for approval of all three volumes.

7.) Exclusion of NYHA Class IV patients from the safety study will likely limit your labeling claims. It is noted that you one time stated that “subjects enrolled in the study may progress to NYHA Class IV during the study which could provide experience with NYHA Class IV patients”. However, this data did not appear to be submitted (or analyzed) as part of this PMA.

8.) Other Issues with the Study (not related to the catheter, primary endpoint)

- It is noted that not many darker-skinned patients were included in the study. In particular South East Asians and African Americans appear to be under represented. This could also be an issue in regards to the refill procedure as it could be more difficult to perform refills in darker skinned individuals; in addition, darker-skinned South East Asians, African Americans and Latinos have a higher tendency to produce keloid scarring. Please justify how the study population reflects the racial and ethnic diversity of PAH patients in the US and explain how all patients will be able to utilize the RIS system.
- Please provide justification for why 7 patients were enrolled into the study with pneumonia at baseline. Please also explain whether these same seven patients experienced excessive infections or other adverse events during the study.
- It appears as though somewhere between 9 (minimum) and 15 (maximum) patients had cardiac rhythm disturbances upon entering the study (from the baseline cardiac characteristics). However, from the presentation of the data, the absolute number of patients with arrhythmias cannot be determined as one patient may have more than one type of arrhythmia; please characterize the arrhythmia data so that it indicates how many patients (N and %) had history of an arrhythmia upon study entry; also compare this to the number (N & %) observed during the study and explain how the risk of arrhythmias is minimized for implantation (since this and other cardiac AEs can obviate the presumed benefits of the RIS system if they prove to be fatal or life threatening). Analyze the cardiac rhythm-related adverse events in the study with what was present at baseline and what would be generally expected in the PAH population.
- There were 100 study deviations were reported during the study; of these deviations, 7 pumps were not implanted per protocol. Since 7 out of 60 is a considerable number describe why this occurred so often and discuss the potential impact.
- It is observed, by reading the study deviation descriptions, that many (at least 21) refill procedures in the study were completed outside of the time period states in the protocol; please provide an analysis of the refills in the study in which you characterize and compare the refills done both within and outside of the stated timelines. This analysis should characterize the refills outside and within the appropriate windows and correlate them to both adverse effects, six minute walk time, and /or other relevant attributes that were measured in this study.

- It is noted that presentation of the study deviations does not make it clear whether these deviations occurred more in one site or whether more than one study deviation was attributed to a patient. You should provide a presentation of the study deviations by study site and by patient (e.g. How many patients were involved [i.e. is the same patient who was not consented the same one who also did not meet the exclusion criteria)? Currently it is only presented by type of deviation.

9.) Pump accuracy, flow rate: The calculation of the accuracy of the pump appears acceptable on its surface; however, it is difficult to ascertain how this aspect of device performance impact the thermal function and dose accuracy issues. It would be helpful if the Sponsor provided an analysis of pump accuracy that also took flow rate, “device malfunctions” (including under-dosing that has been recorded) and the spectrum of adverse events associated with under and over-dosing of Remodulin into account. Without this type of integrated clinical evaluation, the “pump accuracy” data is relatively meaningless.

10.) System modification: Please explain why and how seven systems were “modified” in your response along with a site breakdown indicating at which sites the modifications occurred. It is noted that there were several modifications listed under one patient ID number. Please explain the sequence of events that led to this any describe any sequelae.

11.) Labeling: The submission utilizes a combination of labeling for the previously approved SynchroMed system as well as elements of Remodulin drug labeling and other new elements. The changes are not tracked or highlighted. Clinically, in light of the many changes to the pump system and other critical clinical issues in this submission, the currently proposed labeling cannot be adequately evaluated without comparison to previous labeling and further data as noted in the deficiencies relayed regarding this application. The next version of the Proposed Labeling with all changes clearly indicated (via track changes) should be submitted for Agency evaluation.

That said, the following are provide for your consideration when submitting the next (track changes) version of the proposed device labeling.

In Volume 29, (pages 241- 257) Page 250 of the Labeling document in the submission, the clinical study, safety endpoint and efficacy are discussed. It is noted that currently, inclusion of this section is inappropriate and misleading. If the PMA application is eventually approved for use, you must clearly point out the fact and address the fact that they used a different catheter for the Clinical study. In addition, (b) (4)

the Agency does not agree that the current presentation of safety data is adequate for inclusion in this labeling.

(b) (4)

Technical Manual:

- a. **Adverse event presentation: Volume 29, page 34 in Section 4** Indications, contraindications, and adverse Events – in sub-section 4.3 of the labeling Technical manual, AEs are presented in table format but are not discussed. **The breakdown of possible AEs associated with each component of the RIS in Table 8 is not fully informative. It would be much more useful if there were a list (or table) with the AEs most likely to be seen with the RIS versus the SynchroMed system (and associated implantation procedure, etc.) along with a brief discussion of these events.**

- b. **In Section 5** of the Technical Manual, **the Warnings** preamble states that “Warnings in this chapter apply to the general operation of the system. Warnings that apply to specific steps in the procedure are included in the appropriate instructions. For warnings specific to Remodulin® (treprostinil) Injection, see Section 5.3, (b) (4). Therefore the warning should be re-worded to accurately reflect that use of Remodulin with the system results in component -specific issues that should be considered in addition to the usual system warnings. This warning section should also cross reference Section 8 “Emergency Procedures” since this section contains relevant warnings regarding Remodulin use with the system and specific procedures.

- c. **Section 7 “Drug Information”** states that The Remodulin Implantable System is approved for use with Remodulin in concentrations of (b) (4)

10 mg/mL.

(b) (4)

(b) (4)

(b) (4)

. **Defer to CDER and SEALED.**

- d. **Section 7 under “7.2 Drug refill information”** states that “The maximum refill interval for the Remodulin Implantable System is 112 days (16 weeks). This is a true statement based on the stability of the drug in the RIS system. However, there should be a statement that the interval between refills will usually be shorter than this and the refill schedule should be based on the patient’s dose and should be determined by the patient’s physician
- e. **Section 8.2.2 Remodulin pocket fill procedure** If you suspect a Remodulin pocket fill, perform the following actions, as necessary; the headers for these procedures should probably contain the word(s) Urgent or Emergent – so it would read “ 8.2.2 URGENT procedure for Remodulin pocket fill”
- f. Technical Manual states that: “Remodulin should only be chilled one time. Remodulin that has been chilled and returned to room temperature should not be re-chilled.” Explain the technical basis for this comment.
- g. **Section 13.1 Refilling and programming the pump** of the Technical Manual, the refilling procedure describes use of the template used to determine the correct orientation of the pump. Has this template been tested using a full range off human skin colors?
- h. **Section 15.3 Preparing the new catheter for implant Warning:** Use of catheters may cause trauma to the heart and vasculature. Do not apply force to the catheter during the implant procedure if significant resistance is encountered. Applying force may injure the patient. **It is noted that there are 3 full pages and multiple caveats regarding the proper anchoring of the catheter are noted in the technical Manual. This substantiates our concerns about the need to clinically test catheter Model 8201.**

(b) (4)



If you have any additional questions, please contact Jessica D. Eisner, M.D. at 301-796-5024.

Digital Signature Concurrence Table	
Reviewer Sign-Off	

APPEARS THIS WAY ON ORIGINAL

Appendix A:

Table 1-5: Comparison of Market Release Catheters to Model 8201 Catheter

Feature	Model 8731SC	Ascenda Models 8780 and 8781	Model 8201 Catheter (subject of this PMA)
Catheter drug delivery location	Intrathecal	Intrathecal	Intravascular
Approvals	Market Approved	Market Approved	Not approved
Catheter Tip	(b) (4)		
Distal exit site			
Pump Connector	Custom sutureless connector to SynchroMed II pump	Custom sutureless connector to SynchroMed II pump	Custom sutureless connector to SynchroMed II pump
Catheter body	(b) (4)		
Number of Lumens	Single	Single	Single
Stabilization/ Fixation	V-wing Anchor	Bi-wing Anchor	Anchor sleeve (2-piece design)
Distal end	Atraumatic/flexible	Atraumatic/flexible	Atraumatic/flexible
Length	Adjustable (trimmable) Maximum 104.1 cm	Adjustable (trimmable) 8780 maximum 114.3 cm 8781 maximum 139.7 cm	80cm, 100cm, 120cm
Catheter diameter	(b) (4)		
Introducer size			
Catheter lumen volume			
Implant time	Chronic	Chronic	Chronic

Appendix B:

Table 3: Data Collection and Study Procedure Requirements at Subject Visits							
STUDY PROCEDURE	Baseline	Implant	1 week Follow-up	6 Week, 3, 6, and 12 Month Follow-up	Unscheduled Follow-up	Long-Term Follow-up	Study Exit
Date of Consent and HIPAA/data protection authorization	√						
Inclusion/Exclusion Criteria	√						
Demographics, Medical History Review	√						
Pregnancy screen (if applicable)	√						
Physical Exam	√			√			
NYHA functional classification	√			√			
Subject/caregiver involvement assessment	√			√			
6MWT	√			√			
Quality of Life Assessments	√			√			
Treatment Satisfaction Survey				√ (6wk, 6mo only)			
Blood Sample Collection for Basic Metabolic Profile	√						
Catheter Implanter Survey		√					
Pump Fill/Refill Data (if necessary)		√	√	√	√	√	√
Fluoroscopy / Radiograph for Verification of Catheter and Pump Placement		√					
Adverse Events	√	√	√	√	√	√	√
Blood Sample Collection for plasma treprostinil level	√		√				
Blood Sample Collection for Plasma treprostinil level (if catheter occlusion suspected)		As needed					
Device Traceability record updates							
Medications							
Pregnancy Notification							
Device Malfunctions							
System Modifications							
Study Deviations							
Death							

Table 4: Subject Visit Schedule			
Visit	Window		
	Window Start (# of days post-implant)	Target (# of days post-implant)	Window End (# of days post-implant)
1 Week Follow-up	5 days	7 days	14 days
6 Week Follow-up	36 days	42 days	49 days
3 Month Follow-up	81 days	91 days	105 days
6 Month Follow-up	183 days	183 days	203 days
12 Month Follow-up	335 days	365 days	395 days
18 Month Follow-up	518 days	548 days	578 days
24 Month Follow-up	700 days	730 days	760 days
30 Month Follow-up	883 days	913 days	943 days

Appendix C: Summary of Ancillary Objectives Results per the submission

Table 3 Summary of Ancillary Objective 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: $0.2\% \pm 19.3\%$ 95% confidence interval: $-4.9 - 5.2\%$																				
To characterize changes in quality of life	CAMPHOR (QoL Scale) change from baseline to 6 months <table border="1"> <thead> <tr> <th></th> <th>Symptom Scale</th> <th>Activity Scale</th> <th>QoL Scale</th> </tr> </thead> <tbody> <tr> <td>Change</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Better</td> <td>19 (33%)</td> <td>10 (18%)</td> <td>18 (32%)</td> </tr> <tr> <td>No Change</td> <td>24 (42%)</td> <td>26 (46%)</td> <td>29 (51%)</td> </tr> <tr> <td>Worse</td> <td>14 (25%)</td> <td>21 (37%)</td> <td>10 (18%)</td> </tr> </tbody> </table> <p>EQ-5D Mean absolute change at 6 months \pm S.D.: -0.01 ± 0.10 95% confidence interval: $-0.04 - 0.02$</p>		Symptom Scale	Activity Scale	QoL Scale	Change				Better	19 (33%)	10 (18%)	18 (32%)	No Change	24 (42%)	26 (46%)	29 (51%)	Worse	14 (25%)	21 (37%)	10 (18%)
	Symptom Scale	Activity Scale	QoL Scale																		
Change																					
Better	19 (33%)	10 (18%)	18 (32%)																		
No Change	24 (42%)	26 (46%)	29 (51%)																		
Worse	14 (25%)	21 (37%)	10 (18%)																		
To characterize the incidence of adverse events	Subject experience included 64 enrolled subjects, and 120.7 years of implanted follow-up time in 60 subjects. During that time, there were 737 Adverse Events: 29 complications related to procedure, drug pump, catheter, programmer, Remodulin Injection, refill process, catheter patency test, implant tools, or Model 8540 Catheter Access Port Kit 232 observations related to procedure, drug pump, catheter, programmer, Remodulin Injection, refill process, catheter patency test, implant tools, or Model 8540 Catheter Access Port Kit 476 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: <ul style="list-style-type: none"> 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. 																				
Objective	Results																				
To assess pump fluid delivery accuracy	Percentage of refills with acceptable refill accuracy (1108 out of 1109 refills): 99.9% Accuracy ratio per pump (mean \pm s.d.): 0.93 ± 0.04																				
To assess subject/caregiver involvement in system management	Subject (n=60) mean \pm s.d. hours per week Pre-implant (external pump): 2.49 ± 1.74 hrs 6 months post-implant (internal pump): 0.59 ± 0.83 hrs Mean difference: -1.9 hrs. 95% confidence interval: $-2.42 - -1.32$ P<0.0001																				
To characterize plasma treprostiniil concentration change	Treprostiniil concentration levels increased by an average of: $2.3 \pm 41.0\%$ from pre-implant (with external pump) to one week post-implant.																				

Appendix D:

Table 13: Post-Implant Adverse Events Not Related to the System with 3 or More Occurrences

Preferred Term	Number of AE's (Number of Subject, %)
Implant site pain	45 (43, 71.7 %)
Upper respiratory tract infection	27 (19, 31.7 %)
Pulmonary arterial hypertension	21 (14, 23.3 %)
Injection site reaction	17 (12, 20.0%)
Dyspnoea	17 (11, 18.3 %)
Headache	15 (12, 20.0%)
Fatigue	12 (11, 18.3 %)
Injection site pain	12 (9, 15.0%)
Dizziness	11 (10, 16.7 %)
Hypotension	11 (9, 15.0%)
Immediate post-injection reaction	11 (9, 15.0%)
Nasopharyngitis	11 (9, 15.0%)
Implant site bruising	10 (10, 16.7 %)
Nausea	10 (10, 16.7 %)
Pain in extremity	10 (10, 16.7 %)
Fluid overload	10 (6, 10.0%)
Dyspnoea exertional	9 (7, 11.7 %)
Urinary tract infection	9 (5, 8.3 %)
Flushing	8 (8, 13.3 %)
Abdominal pain	7 (7, 11.7 %)
Back pain	7 (7, 11.7 %)
Palpitations	7 (6, 10.0%)
Pneumonia	7 (6, 10.0%)
Diarrhoea	6 (6, 10.0%)
Vomiting	6 (6, 10.0%)
Oedema peripheral	6 (5, 8.3 %)
Syncope	6 (5, 8.3 %)
Sinusitis	6 (4, 6.7 %)
Anxiety	5 (4, 6.7 %)
Atrial fibrillation	5 (4, 6.7 %)
Hypokalaemia	5 (4, 6.7 %)
Musculoskeletal pain	5 (4, 6.7 %)
Adverse drug reaction	4 (4, 6.7 %)
Arthralgia	4 (4, 6.7 %)
Constipation	4 (4, 6.7 %)
Insomnia	4 (4, 6.7 %)
Pruritus	4 (4, 6.7 %)
Rash	4 (4, 6.7 %)
Right ventricular failure	4 (4, 6.7 %)
Tachycardia	4 (4, 6.7 %)
Cough	4 (3, 5.0%)
Hypoxia	4 (3, 5.0%)
Influenza	4 (3, 5.0%)
Anaemia	3 (3, 5.0%)
Bronchitis	3 (3, 5.0%)
Chest pain	3 (3, 5.0%)

Preferred Term	Number of AE's (Number of Subject, %)
Depression	3 (3, 5.0%)
Epistaxis	3 (3, 5.0%)
Fluid retention	3 (3, 5.0%)
Gastritis	3 (3, 5.0%)
Implant site swelling	3 (3, 5.0%)
Myalgia	3 (3, 5.0%)
Presyncope	3 (3, 5.0%)
Rheumatoid arthritis	3 (3, 5.0%)
Urticaria	3 (3, 5.0%)
Vertigo	3 (3, 5.0%)
Vessel puncture site pain	3 (3, 5.0%)
Abdominal discomfort	3 (2, 3.3 %)
Cardiac failure	3 (2, 3.3 %)
Tooth infection	3 (2, 3.3 %)
Injection site discomfort	3 (1, 1.7 %)
Injection site irritation	3 (1, 1.7 %)

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Appendix E



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

Medtronic, Inc.
Ms. Barbara Chiponis
Distinguished Regulatory Affairs Advisor
Medtronic, Inc.
8200 Coral Sea Street NE, M/S MVS11
Mounds View, MN 55112

Re: G100017/R003
Trade/Device Name: Pulmonary Arterial Hypertension Implantable Vasodilator Therapy (PIVoT) system
Dated: December 17, 2014
Received: December 18, 2014
CMS Category: A1
Annual Report Due: January 21, 2015

Dear Ms. Barbara Chiponis:

The Food and Drug Administration (FDA) has reviewed the interim progress report to your Investigational Device Exemption (IDE) application and has determined that additional information is required. Please address the following questions and concerns:

1. The safety analysis (e.g. "Potential PAH AEs") you have provided is cursory and insufficient to adequately evaluate whether this issue may have impacted patient safety or efficacy of the treatment. According to Table 1: Potential PAH AEs per Month throughout Study which was submitted in your response, there were 161 AEs in the study. Please provide a more detailed analysis of AEs & SAEs submitted for the duration of the trial (including prior to noticing that there was a device issue).

For these analyses – at a minimum, please provide:

- a. separate summary tables of AEs (using Medical Dictionary for Regulatory Activities [MedDRA- indicate version]) in order of decreasing frequency by System Organ Class (SOC), High Level Group Term (HLGT), and Preferred Term (PT);
- b. a table of AEs (using PT) broken down by investigative site;
- c. a table listing all reported SAEs (by both HLGT and PT);
- d. all of the raw safety data (e.g. AE verbatim terms the PT term to which they were coded as well as SAE reporting forms with narratives) for all AEs in the study;

- e. a table which lists AEs (by PT) and indicates which of these were determined by the treating Investigator to be "Related", "Probably related", "Possibly related" and of "Unknown" relationship to the device/treatment.

Also present AE data which will indicate when (during the trial and the subject's therapy) the AE occurred relative to the pump being implanted and also refilled. If there were multiple events experienced by one patient, please present this data separately (in table form) in the response.

Finally, include the company's critical, medical analyses of the requested data in a Clinical Safety Summary Report. Please note that in addition to what has been requested above, you may include up to 30 pages of additional data to discuss/explain the potential patient safety impact of this device issue.

2. We have reviewed the CAPA documents provided and are unable to locate any data supporting the conclusion that gas permeation from Remodulin is resulting in under dosing or that the rate of under dosing will stabilize at an accuracy ratio of 0.8. Please amend G100017 to include this information.
3. The chilling procedure for refill of Remodulin is not discussed within the supplement. Please address whether or not the chilling of Remodulin prior to refilling the pump reservoir contributes to the permeation of gas through internal pump tubing via an increase in gas content of the chilled Remodulin being filled into the pump.
4. It is unclear if there is any information to suggest that the rate of permeation is dependent on the solution being delivered. Clarify if the gas permeation is an issue unique to the Remodulin Implanted System. Whether it is expected that this issue would occur regardless of the solution being delivered.
5. It is unclear whether the increased rate of permeation with increased flow rate only include gas permeation, or it is expected that permeation of other substances will occur at increased rate compared to the approved Synchroned system. If the rate of permeation is increased for non-gas substances, please provide an assessment for how this might impact pump reliability.
6. It is uncertain the increased internal pressure will degrade the pump's reliability. Please provide an assessment of how the increased internal pressure might impact pump reliability.

This information must be submitted to FDA within 45 days from the date of this letter. It should be identified as an IDE amendment referencing G100017/R003, and must be submitted in duplicate to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
IDE Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you do not provide this information within 45 days from the date of this letter, we may take steps to propose withdrawal of approval of your IDE application.

If you have any minor clarification questions concerning the contents of the letter, please contact Weihong Gu at 301-796-6973 or Weihong.Gu@fda.hhs.gov.

Sincerely yours,

Erin Keith
Director
Division of Anesthesiology,
General Hospital, Respiratory, Infection
Control, and Dental Devices
Office of Device Evaluation
Center for Devices and Radiological Health

SAFETY UPDATE

NDA#208276

MEDICAL REVIEWER: MARYANN GORDON, MD

Summary

This safety update contains an additional 1.1 years of follow up compared to the follow up reported for the NDA. There were three additional deaths including one which involved a pump malfunction (previously submitted to the Agency as a safety report). This patient had an extensive history of cardiac and pulmonary complications and she died of a cardiac event; it is unlikely that the pump failure contributed to her death. Other deaths and serious adverse events are similar to those reported in the NDA.

Introduction

As of the data cut-off for this report (July 12, 2017), the 60 implanted subjects averaged 4.4 years of follow-up for a total of 264.85 patient-years. All active subjects have completed their four year visit, and 24 have completed their five year visit. The range of individual subject participation was 87 to 2,150 days. In comparison, the NDA had a cut-off date of January 8, 2016, there have been a total of 197 subject-years of documented implanted follow-up time, an average of 3.3 years (range: 87 to 1,625 days) among the 60 implanted subjects.

Primary objective

The primary endpoint of the study was the rate of catheter-related complications per 1000 patient days compared with a published rate of catheter-related complications seen in patients with central venous catheters

Safety

Definitions

A complication is defined as any adverse event (AE) that results in death, involves any termination of significant device function, or requires an invasive intervention. Catheter-related complications included catheter-related systemic bloodstream infections (BSIs), site infections, and complications from catheter thrombosis, mechanical dysfunction, catheter dislocation, and procedure-related pneumothorax complications.

Results

Catheter-related complications

Seven catheter-related complications were observed during the accumulation of 96,670 patient days, resulting in a total of 0.07 catheter related complications per 1,000 patient days compared with the published rate of 0.98 to 2.51 per 1,000 patient days. One subject ^{(b) (6)} had three of the seven catheter-related complications and ultimately had the implanted system explanted as a result of sepsis and pump pocket infection after her third system modification.

Deaths

Fourteen subjects were reported to have died during study participation, one of which was adjudicated as related to pump failure ^{(b) (6)}. This patient had an extensive cardiac and pulmonary history prior to enrollment. She experienced a cardiac arrest and motor stall caused by pump tube displacement, kink, and breach with leak. In this case, death resulting from pump

malfunction seems unlikely. All deaths occurred more than 80 days past implant. Three deaths (hemorrhagic shock, acute cardiac failure, pump failure) were added to the safety update.

Details of all deaths are shown below.

Table 12-18. Subject Deaths

Subject	Days After First Implant	Cause of Death (Preferred Term)
(b) (6)	87	Cardiac failure
	129	Pulmonary embolism
	299	Right ventricular failure
	615	Cardiac failure
	728	Cardiopulmonary failure
	857	Cardiac arrest
	888	Respiratory failure
	995	Haemoptysis
	1139	Pulmonary arterial hypertension
	1420	Pulmonary arterial hypertesion
	1472	Embolic stroke
	1525	Shock haemorrhagic
	1539	Cardiac failure acute
	1745	Pump failure

Source: IndividualAdverseEvents.sas

Bold indicates change from previous data-cut.

Serious AEs

Two hundred five treatment-emergent AEs in 49 subjects were serious (including one serious adverse event (SAE) that occurred during implant). The most common SAEs were pneumonia, atrial fibrillation, and immediate post-injection reaction.

The immediate post-injection reactions have occurred in 7 subjects and included events such as flushing, headache, nausea, and/or hemodynamic changes because of a small amount of Remodulin exiting the re-fill needle as the needle was withdrawn from the pump reservoir during a pump refill. One subject has discontinued the study due to sepsis, which was adjudicated as related to a system modification procedure.

System modifications

There have been a total of 22 system modifications in 17 subjects whereby the catheter and/or pump required invasive modification. Seven of the system modifications were in two subjects because of catheter dislocation, catheter damage, and infection. One system modification involved replacement of the sutureless connector because of a suspected leak but later adjudicated as related to a pocket infection.

There were six of the system modifications because of pump failure and five system

modifications were planned and necessary to replace the system because of depleted pump battery.

Table 12-23. System Modifications

Subject ID	Days Post-implant	Component	What was Done	Reason (Verbatim from eCRF)
(b) (6)	1729	SynchroMed II Pump	Explanted, Replaced	Pump Battery Depletion, Expected
	1752	SynchroMed II Pump	Explanted, Replaced	Pump Failure Occurred
	2093	SynchroMed II Pump	Explanted, Replaced	Pump Battery Depletion, Expected
	23	Model 10642 Catheter SynchroMed II Pump	Explanted, Replaced Explanted, Replaced	Catheter Dislocation / Dislodgement
	426	Model 10642 Catheter SynchroMed II Pump	Explanted, Replaced Explanted, Replaced	Possible Leak in Catheter
	1050	Model 10642 Catheter SynchroMed II Pump	Explanted, Replaced Explanted, Replaced	Possible Catheter Leak

Subject ID	Days Post-implant	Component	What was Done	Reason (Verbatim from eCRF)
	1066	Model 10642 Catheter SynchroMed II Pump	Explanted, Not Replaced Explanted, Not Replaced	Catheter Incision Site Infection , Pump Pocket Infection Occurred, Sepsis Occurred
(b) (6)	1926	SynchroMed II Pump	Explanted, Replaced	Pump Battery Depletion, Premature
	2087	Model 10642 Catheter SynchroMed II Pump	Explanted, Not Replaced Explanted, Not Replaced	Pump Pocket Infection Occurred , Incision Dehiscd
	1831	SynchroMed II Pump	Explanted, Replaced	Pump Failure Occurred
	232	SynchroMed II Pump	Repositioned	Sutureless Connector Change Out Only, Due to Suspected Leak
	1356	SynchroMed II Pump	Explanted, Replaced	Pump Battery Depletion, Expected
	1665	SynchroMed II Pump	Explanted, Replaced	Pump Failure Occurred
	1535	SynchroMed II Pump	Explanted, Replaced	Low Pump Accuracy Ratio
	1736	SynchroMed II Pump	Explanted, Replaced	Pump Failure Occurred
	11	Model 10642 Catheter	Explanted, Replaced	Catheter Dislocation / Dislodgement
	49	Model 10642 Catheter	Explanted, Replaced	Catheter Dislocation / Dislodgement
	1624	SynchroMed II Pump	Explanted, Replaced	Pump Failure Occurred
	1489	Model 10642 Catheter SynchroMed II Pump	Explanted, Not Replaced Explanted, Not Replaced	Bilateral Lung Transplant
	1610	SynchroMed II Pump	Explanted, Replaced	Pump Battery Depletion, Expected
	1562	SynchroMed II Pump	Explanted, Replaced	Pump Battery Depletion, Expected
	1749	SynchroMed II Pump	Explanted, Replaced	Pump Battery Depletion, Expected

Source: [SystemModifications.sas](#)

Bold indicates change from previous data-cut.

All but three subjects had their pump explanted and replaced.

All adverse events

A total of 1248 treatment emergent (including 2 during implant and 1246 post-implant) AEs had been reported in 60 subjects at the time of the data cut off. The most common post-implant AEs were upper respiratory tract infection, implant site pain, worsening PAH, dyspnea, injection site reaction, headache, nasopharyngitis, immediate post-injection reaction, hypotension, fluid overload, nausea, atrial fibrillation, pneumonia, injection site pain, dizziness, fatigue, and sinusitis.

Table 12-2. Most Frequently Encountered Post-implant Adverse Events Reported in 10% or More of Subjects

Preferred Term	08Jan2016 Cut-off		19Jul2016 Cut-off		12Jul2017 Cut-off	
	Number of Patients (%) N=60	Number of Events	Number of Patients (%) N=60	Number of Events	Number of Patients (%) N=60	Number of Events
Upper respiratory tract infection	29 (48)	53	30 (50)	56	32 (53)	63
Implant site pain	46 (77)	48	46 (77)	48	46 (77)	48
Pulmonary arterial hypertension ^a	20 (33)	35	20 (33)	37	22 (37)	40
Dyspnoea	18 (30)	26	20 (33)	28	20 (33)	28
Injection site reaction ^b	15 (25)	21	15 (25)	22	16 (27)	25
Headache	16 (27)	22	18 (30)	24	18 (30)	24
Nasopharyngitis	12 (20)	17	15 (25)	20	16 (27)	23
Immediate post-injection reaction ^c	12 (20)	16	13 (22)	17	16 (27)	22
Hypotension	14 (23)	16	14 (23)	16	16 (27)	19
Fluid overload	8 (13)	17	8 (13)	18	8 (13)	18
Nausea	16 (27)	16	17 (28)	18	17 (28)	18
Atrial fibrillation	5 (8)	16	5 (8)	16	6 (10)	18

Preferred Term	08Jan2016 Cut-off		19Jul2016 Cut-off		12Jul2017 Cut-off	
	Number of Patients (%) N=60	Number of Events	Number of Patients (%) N=60	Number of Events	Number of Patients (%) N=60	Number of Events
Pneumonia	11 (18)	13	12 (20)	15	14 (23)	18
Injection site pain ^d	13 (22)	17	13 (22)	17	13 (22)	17
Dizziness	13 (22)	15	14 (23)	16	14 (23)	16
Fatigue	14 (23)	15	14 (23)	15	14 (23)	15
Sinusitis	8 (13)	11	9 (15)	12	11 (18)	15
Urinary tract infection	7 (12)	12	8 (13)	13	9 (15)	14
Bronchitis	11 (18)	11	12 (20)	13	12 (20)	13
Pain in extremity	12 (20)	12	12 (20)	12	13 (22)	13
Diarrhoea	9 (15)	10	9 (15)	11	11 (18)	13
Hypokalaemia	6 (10)	8	7 (12)	10	7 (12)	12
Implant site bruising	10 (17)	10	10 (17)	10	10 (17)	11
Palpitations	6 (10)	9	6 (10)	9	7 (12)	11
Abdominal pain	9 (15)	9	9 (15)	9	10 (17)	10
Flushing	9 (15)	9	9 (15)	9	10 (17)	10
Oedema peripheral	6 (10)	8	6 (10)	8	7 (12)	10
Syncope	6 (10)	7	7 (12)	8	9 (15)	10
Anxiety	8 (13)	9	8 (13)	9	8 (13)	9
Dyspnoea exertional	7 (12)	9	7 (12)	9	7 (12)	9
Vomiting	9 (15)	9	9 (15)	9	9 (15)	9
Influenza	6 (10)	7	8 (13)	9	8 (13)	9

Other Serious Adverse Events

A total of 204 SAEs were reported post implant in 49 of the 60 implanted subjects. Additionally, one SAE (pneumothorax) occurred during implant, and 5 SAEs occurred pre-implant (four infections one atrial flutter).

Table 12-19. Post-implant SAEs Occurring in at Least Two Subjects

Preferred Term	08Jan2016 Cut-off		19Jul2016 Cut-off		12Jul2017 Cut-off	
	Number of Patients (%) N=60	Number of Events	Number of Patients (%) N=60	Number of Events	Number of Patients (%) N=60	Number of Events
Pneumonia	8 (13)	10	10 (17)	12	10 (17)	13
Atrial fibrillation	4 (7)	9	4 (7)	9	4 (7)	9
Immediate post-injection reaction ^a	7 (12)	9	7 (12)	9	7 (12)	9
Gastrointestinal haemorrhage	1 (2)	1	2 (3)	4	4 (7)	7
Device malfunction	0 (0.0)	0	0 (0.0)	0	6 (10)	6
Fluid overload	4 (7)	5	4 (7)	5	4 (7)	5
Syncope	2 (3)	2	3 (5)	3	5 (8)	5
Cardiac failure	4 (7)	4	4 (7)	4	4 (7)	4
Right ventricular failure	3 (5)	4	3 (5)	4	3 (5)	4
Atrial tachycardia	2 (3)	2	3 (5)	3	3 (5)	4
Pulmonary arterial hypertension	2 (3)	2	3 (5)	3	4 (7)	4
Respiratory failure	1 (2)	1	3 (5)	3	3 (5)	4
Chest pain	3 (5)	3	3 (5)	3	3 (5)	3
Hypotension	2 (3)	3	2 (3)	3	2 (3)	3
Lead dislodgement	2 (3)	3	2 (3)	3	2 (3)	3
Bronchitis	2 (3)	2	2 (3)	3	2 (3)	3
Dyspnoea	2 (3)	2	3 (5)	3	3 (5)	3
Acute kidney injury	1 (2)	1	1 (2)	2	2 (3)	3
Clostridium difficile colitis	2 (3)	2	2 (3)	2	2 (3)	2
Injection site reaction ^b	2 (3)	2	2 (3)	2	2 (3)	2

Preferred Term	08Jan2016 Cut-off		19Jul2016 Cut-off		12Jul2017 Cut-off	
	Number of Patients (%) N=60	Number of Events	Number of Patients (%) N=60	Number of Events	Number of Patients (%) N=60	Number of Events
Pericardial effusion	2 (3)	2	2 (3)	2	2 (3)	2
Pneumothorax	2 (3)	2	2 (3)	2	2 (3)	2
Supraventricular tachycardia	2 (3)	2	2 (3)	2	2 (3)	2
Deep vein thrombosis	1 (2)	1	2 (3)	2	2 (3)	2
Rhinovirus infection	1 (2)	1	1 (2)	1	2 (3)	2

^aImmediate post-injection reaction was used when the subject experienced a constellation of systemic symptoms post refill (flushing, headache, nausea, and / or hemodynamic changes) due to a small amount of Remodulin exiting the needle as the needle is withdrawn from the pump reservoir.

^bInjection site reaction was used when the subject experienced a constellation of local symptoms at or around the refill site (pain, erythema, and / or swelling) due to a small amount of Remodulin exiting the needle as the needle is withdrawn from the pump reservoir.

Source: [AEListing.sas](#)

Bold indicates change from previous data-cut.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARYANN GORDON
04/26/2018

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208276
Priority or Standard	S
Submit Date(s)	December 16, 2015
Received Date(s)	December 16, 2015
PDUFA Goal Date	October 16, 2016
Division / Office	ODE1/DCRDP
Reviewer Name(s)	Maryann Gordon, MD Christine Garnett, Pharm.D. (safety)
Review Completion Date	August 3, 2016
Established Name	treprostinil
(Proposed) Trade Name	Remodulin® Implantable System
Therapeutic Class	prostacyclin vasodilator
Applicant	Medtronic
Formulation(s)	chronic intravenous infusion
Dosing Regimen	Undiluted Remodulin is administered intravenously via the Remodulin Implantable System. The initial dose of Remodulin with the Remodulin Implantable System should be the same as the dose the patient was receiving using the external infusion pump
Indication(s)	Pulmonary arterial hypertension WHO Group I
Intended Population(s)	Patients who are currently receiving Remodulin® administered via an external infusion pump

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical primary reviewers are recommending approval of the use of Remodulin (treprostinil) with an implantable pump and catheter in patients with pulmonary arterial hypertension (PAH) pending approval of the device by CDRH.

The Remodulin Implantable System (RIS) is intended to deliver Remodulin in the treatment of patients with PAH who meet the approved Remodulin Injection indication, using the approved formulation, and approved intravenous route of administration. The single uncontrolled, open label trial provides adequate support for the use of the implanted device.

The data generated by the sole clinical trial G100017 provide adequate safety information to support approval of the NDA supplement from United Therapeutics to support updates to Remodulin Injection labeling.

1.2 Risk Benefit Assessment

Current options allow patients with PAH continuous parenteral prostacyclin therapy via an external infusion pump, either with an indwelling central venous catheter or by subcutaneous injection. Indwelling central venous catheters are associated with the risk of blood stream infections and sepsis, which can be fatal. Patients receiving subcutaneous injections, the preferred route of administration, often experience severe infusion site pain.

In an open-label study of IV treprostinil (n=47), there were seven catheter-related line infections during approximately 35 subject-years, or about 1 blood stream infection (BSI) per 5 years of use. A CDC survey of seven sites that used IV treprostinil for the treatment of PAH found approximately 1 BSI (defined as any positive blood culture) event per 3 years of use.

Administration of IV Remodulin with a high pH glycine diluent such as Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium has been associated with a lower incidence of BSIs when compared to neutral diluents (sterile water, 0.9% sodium chloride) when used along with catheter care guidelines.

While the use of the RIS may lessen the risk of blood stream infection, the data only support the use of the implantable pump for convenience and esthetic reasons.

1.2 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None regarding the infused drug, Remodulin.

1.4 Recommendations for Postmarket Requirements and Commitments

None regarding the infused drug, Remodulin.

2 Introduction and Regulatory Background

2.1 Product Information

The RIS is a programmable, implantable drug delivery system for chronic intravenous infusion of Remodulin in subjects with PAH.

The RIS includes:

- Model 8201 Implantable Intravascular Catheter
- Model 8637 SynchroMed II Programmable Pump for RIS (CFNs 8637P20 and 8637P40)
- Model 8840 N'Vision Clinician Programmer and Model 8870 Application Card including RIS software application.

Principles of Operation

Remodulin enters RIS implantable infusion pump (the “pump”) through the reservoir fill port and passes through the reservoir over pressurization valve and into the pump reservoir. At normal body temperatures, propellant exerts pressure on the reservoir bellows which contain the drug. This pressure advances drug into the pump tubing. The battery-powered electronics and motor precisely delivers the programmed dose out through the catheter port and into the Remodulin Implantable System intravascular catheter. The peristaltic action of the pump moves the drug from the pump reservoir, through the pump tubing, check valve, catheter port, and implanted catheter, to the infusion site.

Remodulin (treprostinil) Injection

Remodulin Injection is a sterile sodium salt formulated for continuous subcutaneous or intravenous (IV) administration. Remodulin, approved on May 21, 2002, is a prostanoid therapy for treating PAH subjects.

Remodulin Injection is administered via an external infusion pump and surgically placed central venous catheter.

Remodulin is currently FDA approved for the same subject population and route of delivery. The use of Remodulin in the RIS does not change the drug’s indicated subject population, drug dosage, formulation or route of administration for which the drug has already received FDA approval.

3 Ethics and Good Clinical Practices

3.1 Compliance with Good Clinical Practices

Each study site consulted an Institutional Review Board (IRB), a review panel that was responsible for ensuring the protection of the rights, safety and well-being of human subjects

involved in a clinical investigation. The sponsor ensured that each IRB consulted was adequately constituted to provide assurance of that protection.

3.2 Financial Disclosures

Information collected on Form FDA 3454 entitled “Certification: Financial Interests and Arrangements of Clinical Investigators” and Form FDA 3455 (expiration December 31, 2015) entitled “Disclosure: Financial Interests and Arrangements of Clinical Investigators” follow. These forms pertain to the investigators and co-investigators directly involved in the treatment or evaluation of research subjects conducted under IDE G100017. There were 5 of 50 (10%) investigators for whom Medtronic was unable to collect financial disclosure despite acts of due diligence to obtain the information. The majority of the forms that were unable to be collected were due to the investigator leaving the study center. In the case where an Investigator was no longer at the study center and the forwarding address was left at the previous center or the Investigators address was available, 2 certified letters were sent to the Investigator to attempt to collect the Financial Disclosure information.

Medtronic has determined that the investigators listed on Form 3454 have not entered into any financial agreement whereby the value of the compensation could affect the outcome of the study. For those investigators who either reported significant payments from Medtronic and/or United Therapeutics, equity ownership, and/or proprietary interest, individual statements on Form 3455 have been provided. The determination that they have received no significant payments from Medtronic was made by reviewing Medtronic accounts payable information and written confirmation directly from the investigators. Medtronic does not believe that these financial arrangements have introduced bias to the results of the DelIVery for PAH clinical investigation (G100017). There is no indication that this is inaccurate.

Form FDA 3454 (4/13): The following is a list of Investigators/Co-Investigators for the DelIVery for PAH Clinical Evaluation for Form FDA 3454 (4/13) checkbox (1):

Name Location



(b) (6)

Clinical Review

Reviewers: M Gordon, C Garnett

NDA#208276

(b) (6)



Clinical Review

Reviewers: M Gordon, C Garnett

NDA#208276

(b) (6)

The following is a list of Investigator/Co-Investigator for the DelIVery for PAH Clinical Evaluation where a Financial Disclosure Form was unable to be obtained. It was confirmed that these Investigators/Co-Investigators participated in study related activities and per Medtronic Accounts Payable department, no significant payments were made.

Name Location

(b) (6)

Form FDA 3455 (4/13) entitled “Disclosure: Financial Interests and Arrangements of Clinical Investigators”

Financial information was obtained for all investigators directly involved in the treatment or evaluation of research subjects.

- (b) (6) reported receiving consulting fees, honoraria, and advisory board payments from United Therapeutics in excess of \$25,000 since the start of the study in 2011.
- (b) (6) reported receiving compensation for work performed to complete the study (meetings, pump implants, refills, and follow-up assessments) from Medtronic in excess of \$25,000 since the start of the study in 2011; however, the money was reimbursed (b) (6) to cover expenses.
- (b) (6) reported receiving consulting fees from Medtronic in excess of \$25,000 as well as honoraria from United Therapeutics in excess of \$25,000 since the start of the study in 2011.

5 Sources of Clinical Data

The DelIVery for PAH study was a multi-center, prospective, single arm, non-randomized, open label study designed to evaluate the safety of the Model 10642 Implantable Intravascular Catheter used with the RIS in the treatment of PAH. The safety profile of the newly developed implantable catheter was established when utilized with the commercially available components in the RIS.

6 Review of Efficacy**6.1 Indication**

The primary objective of this study 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.

6.1.1 Methods

Overall Study Design and Plan

The DelIVery for PAH study enrolled subjects who were receiving Remodulin per the indication in the Remodulin package label¹. Subjects were required to have been on IV Remodulin, and to have a stable dose of Remodulin for at least 4 weeks prior to enrollment. Implant of the system occurred within two weeks of the baseline visit². To maintain IV Remodulin delivery during the implant procedure, subjects had a temporary external drug delivery line (peripheral IV, midline catheter, or peripherally inserted central catheter [PICC]) at least one day prior to implantation of the system. A successful implant included implant of the SynchroMed II Implantable Infusion System and the Implantable Intravascular catheter, and completion of the prime bolus procedure.

After the prime bolus procedure was completed, the pump delivered drug at the subject's prescribed therapeutic rate, and the subject was transitioned off the external delivery system. 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. Subjects were also seen at unscheduled follow-up visits as needed, primarily for pump refills, Remodulin drug dose change, and adverse events.

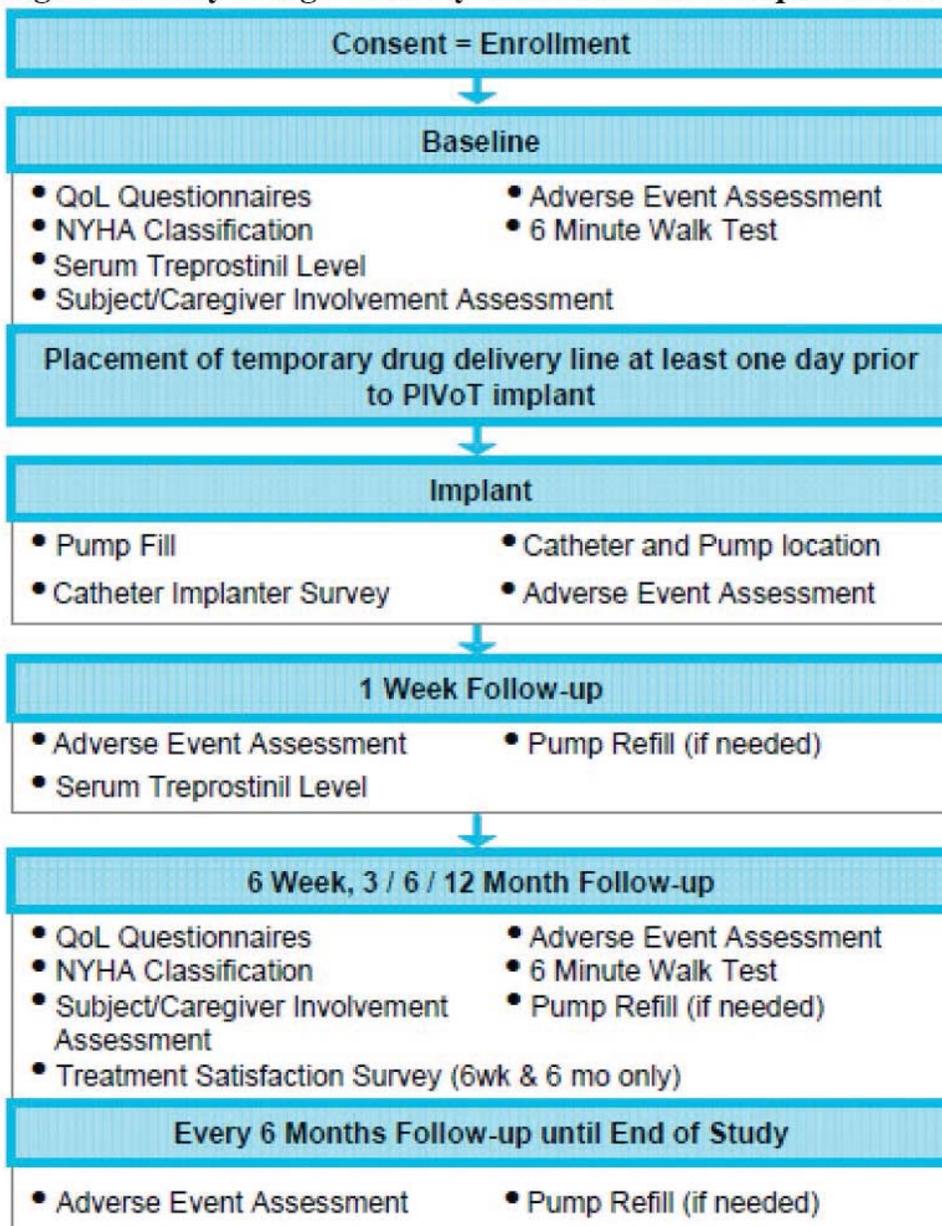
Figure 1. Study Design and Key Data Collection Requirements

¹ 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 subjects 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%) (1.1)
- Subjects 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. (1.2)

² study sites were required to have the following staff physicians (a physician may have filled more than one of these roles): a) physician who is proficient in managing SynchroMed II Implantable Infusion System, b) physician who regularly implants cardiac leads or vascular catheters, c) Health Care Professional who is proficient with SynchroMed II Implantable Infusion System filling procedure.

Figure 1 Study Design and Key Data Collection Requirements



Blood Sample Collection

At baseline and one week follow-up, a blood sample was required to be collected for analysis of plasma treprostinil levels. These samples were required to be drawn at approximately the same time of day.

Catheter Imaging Sub-Study

The objective of the DelIVery for PAH Catheter Imaging Sub-Study was to collect high quality medical images to measure catheter shape change in the Model 10642 Implantable Intravascular Catheter during a given set of subject positions through the use of x-ray imaging.

A total of 20 subjects were enrolled at 3 sites in the sub-study.

Pump Refills

Pump refill procedures occurred at scheduled or protocol defined unscheduled visits depending on the volume of drug in the pump reservoir and the individual subject's infusion rate. Refill schedules ranged from 8-12 weeks.

Catheter Patency Test

A catheter patency test was to be performed if a subject had a suspected catheter occlusion adverse event.

Inclusion Criteria

- Subject is 18 years of age or older
- Subject (or subject's legally authorized representative) is willing and able to provide written informed consent
- Subject is willing and able to comply with the protocol, including required follow-up visits
- Subject 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
- Subject is receiving continuous infusion of Remodulin therapy via intravenous delivery using an external drug delivery pump system. Subject has been at a stable Remodulin dose (no change in dose) for at least four weeks
- Subject's anticoagulation therapy can be managed to permit safe device implantation
- Subject has no history of pulmonary embolism since the initiation of subcutaneous or IV therapy for PAH.

Exclusion Criteria

- Subject is a woman who is pregnant, nursing, or of child bearing potential and is not on a reliable form of birth control

- Subject 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
- Subject has been initiated on a new oral PAH therapy in the last two months
- Subject has had a recent (within three months) or otherwise unresolved infection requiring antibiotic treatment
- Subject is diagnosed with PAH associated with hemoglobinopathies (sickle cell anemia, thalassemia), HIV, schistosomiasis, portal hypertension, pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis
- Subject 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
- Subject 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
- Subject is a person for whom the implantable vascular catheter length of 80 cm was excessively long or too short to be properly implanted
- Subject has an existing external catheter(s) that would remain in place after the pump implant
- Subject is a person for whom the implantable pump cannot be implanted 2.5 cm or less from the skin surface
- Subject is a person whose body size is not sufficient to accept implantable pump bulk and weight
- Subject is at increased susceptibility to systemic or soft tissue infections as determined by physician
- Subject is Functional Class IV (*New York Heart Association (NYHA)*)

Objectives

The primary 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 ancillary objectives were:

- To characterize percent change of six-minute walk test distance from baseline to six weeks post-implant
- To characterize changes in quality of life
- To characterize the incidence of adverse events
- To characterize healthcare utilization (hospitalizations, emergency room visits, and urgent clinic visits)

- To assess pump fluid delivery accuracy
- To assess subject/caregiver involvement in system management
- To characterize plasma treprostinil concentration change

The Adverse Event Advisory Committee (AEAC) was adjudicated all adverse events and subject deaths in accordance with the “DelIVery for PAH” protocol as well as Medtronic and geographic-specific operational and regulatory requirements. The AEAC consisted of four non-Medtronic employed physicians in the US representing cardiology/PAH, vascular surgery, and anesthesiology/pain management. None of the AEAC members were “DelIVery for PAH” clinical investigators.

The primary endpoint was catheter-related complications per 1000 subject days. The AEAC adjudicated all adverse events and determined whether an event with relatedness or unknown relatedness to the catheter was a complication or an observation.

Table 1. Unavoidable AEs Related to Implant Procedure

Table 5: Unavoidable 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

Table 2. Relatedness Definitions

Relatedness	
Procedure-related	An adverse event that occurs due to any procedure related to the implantation or surgical modification of the system
Refill process-related	An adverse event that results from the process of refilling the implantable drug infusion pump
Catheter patency test-related	An adverse event that results from performing the catheter patency test
Catheter-related	An adverse event that results from the presence or performance (intended or otherwise) of the Implantable Intravascular Catheter, Model 10642

Drug-related	An adverse event that results from the presence or performance (intended or otherwise) associated with the use of the drug (Remodulin Injection). This includes all cases of lack of efficacy, overdose, drug abuse and misuse, drug maladministration or accidental exposure and dispensing errors. It also includes all cases of drug-drug interaction
Infusion pump-related	An adverse event that results from the presence or performance (intended or otherwise) of the Implantable Drug Infusion Pump
CAP kit-related	An adverse event that results from the presence or performance (intended or otherwise) of the CAP kit.
Programmer-related	An adverse event that results from the presence or performance (intended or otherwise) of the programmer
Implant Tool-Related	An adverse event that results from the presence or performance (intended or otherwise) of the implant, introduction, or tunneling tool

If an adverse event indicated that there was unknown relatedness to the catheter, and the event was classified as a complication, it was counted as a catheter related complication. Additionally, in the event a pneumothorax was adjudicated by the AEAC as procedure-related, and the event was classified as a complication, it was counted toward the primary objective.

The number of subject days contributed by each subject was the latest known date of follow-up (from a follow-up eCRF, adverse event eCRF, or exit eCRF) minus the implant date for successfully implanted subjects

The data in this report includes any visit or event that occurred on or before July 25, 2014 with data received by August 8, 2014. The database was frozen on August 28, 2014.

The number of catheter-related complications per 1000 patient days was estimated using all subjects with an implant attempt. A one-sample exact test for the Poisson rate was used to obtain the 97.5% one sided upper confidence bound of the catheter-related complications.

6.2 Efficacy Results

6.2.1 Demographics

The following Tables present baseline information for all 64 subjects enrolled, including the four subjects who left the study prior to implant, and the 60 subjects who were implanted.

Table 3. Baseline Demographics

Table 18 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

The majority of subjects were female and the average age was approximately 50 years (range 24-74).

Baseline PAH Disease

The table below shows the baseline characteristics of the underlying disease. Majority (57%) of subjects had idiopathic PAH. The total mean daily dose of study drug was 72 ng/kg/min.

Table 4. Baseline PAH Disease

Table 19 Baseline PAH Disease

Baseline Subject Characteristics	Non-implanted Subjects (n = 3)	Implanted Subjects (n = 60)	Total Subjects (n = 63)
Classification of PAH (n, %)			
Idiopathic	1 (33%)	35 (58%)	36 (57%)
Heritable	0 (0%)	2 (3%)	2 (3%)
Associated	2 (67%)	23 (38%)	25 (40%)
Current total daily dose of Remodulin (ng/kg/min)			
Mean ± Standard Deviation	88.3 ± 62.1	71.4 ± 27.8	72.2 ± 29.5
Median	55.0	68.0	67.0
25 th Percentile - 75 th Percentile	50 - 160	48 - 92	49 - 92
Minimum – Maximum	50 - 160	22 - 142	22 - 160

Table 4 (continued)

Baseline Subject Characteristics	Non-implanted Subjects (n = 3)	Implanted Subjects (n = 60)	Total Subjects (n = 63)
Hours per week spent managing system (subject)			
Mean ± Standard Deviation	3.5 ± 0.9	2.5 ± 1.7	2.5 ± 1.7
Median	4.0	2.0	2.0
25 th Percentile - 75 th Percentile	3 - 4	1 - 3	1 - 4
Minimum – Maximum	3 - 4	0 - 8	0 - 8
Hours per week spent managing system (caregiver)			
Mean ± Standard Deviation	1.3 ± 2.3	1.0 ± 1.5	1.0 ± 1.5
Median	0.0	0.0	0.0
25 th Percentile - 75 th Percentile	0 - 4	0 - 2	0 - 2
Minimum – Maximum	0 - 4	0 - 5	0 - 5
Is the subject taking supplemental oxygen? (n,%)			
No	3 (100%)	29 (48%)	32 (51%)
Yes, as needed	0 (0%)	3 (5%)	3 (5%)
Yes, at night (sleep)	0 (0%)	14 (23%)	14 (22%)
Yes, continuously	0 (0%)	9 (15%)	9 (14%)
Yes, other ¹⁸	0 (0%)	5 (8%)	5 (8%)
NYHA Classification (n,%)			
Class I	0 (0%)	10 (17%)	10 (16%)
Class II	2 (67%)	30 (50%)	32 (51%)
Class III	1 (33%)	20 (33%)	21 (33%)
Class IV	0 (0%)	0 (0%)	0 (0%)
Six-minute walk test (m)			
N	2	60	62
Mean ± Standard Deviation	388.0 ± 142.7	423.3 ± 98.6	422.2 ± 98.9
Median	388.0	422.0	422.0
25 th Percentile - 75 th Percentile	287 - 489	344 - 494	343 - 493
Minimum – Maximum	287 - 489	134 - 637	134 - 637

The mean hours spent by the subject managing the system was 2.5 and it was 1 hour for caregivers.

The majority of subjects did not receive supplemental oxygen. Most subjects were NYHA class II (51%) or class III (33%). None was class IV and 16% were class I. The baseline 6 minute walk distance was 422 m (range 134-637m).

Table 4 (continued)

Baseline Subject Characteristics	Non-implanted Subjects (n = 3)	Implanted Subjects (n = 60)	Total Subjects (n = 63)
Was the subject previously treated with subcutaneous Remodulin Injection delivery? (n,%)			
Yes	2 (67%)	29 (48%)	31 (49%)
No	1 (33%)	31 (52%)	32 (51%)
Time of external venous catheter implant (months)			
Mean ± Standard Deviation	4.8 ± 3.2	19.8 ± 25.8	19.1 ± 25.4
Median	5.7	9.4	8.9
25 th Percentile - 75 th Percentile	1 - 7	3 - 30	3 - 29
Minimum - Maximum	1 - 7	0 - 141	0 - 141
Type of current chronic external catheter (n,%)			
PICC Line	1 (33%)	21 (35%)	22 (35%)
Central Venous	2 (67%)	34 (57%)	36 (57%)
Other ¹⁹	0 (0%)	5 (8%)	5 (8%)
Catheter introduction vessel (n,%)			
Axillary	0 (0%)	9 (15%)	9 (14%)
Cephalic	0 (0%)	4 (7%)	4 (6%)
Internal Jugular	0 (0%)	28 (47%)	28 (44%)
Subclavian	1 (33%)	12 (20%)	13 (21%)
Other ²⁰	2 (67%)	7 (12%)	9 (14%)
Catheter introduction side (n,%)			
Right	2 (67%)	37 (62%)	39 (62%)
Left	1 (33%)	23 (38%)	24 (38%)
Catheter tip location (n,%)			
SVC - just outside cardiac shadow	0 (0%)	23 (38%)	23 (37%)
SVC - mid	0 (0%)	8 (13%)	8 (13%)
Other ²¹	3 (100%)	29 (48%)	32 (51%)

Slightly more than half had previously been treated with subcutaneous Remodulin. The mean time of external catheter implant was 19 months.

Baseline cardiac history

-3% had previous cardiac arrest

-2% had cardiomyopathy

-6% had congenital heart disease

-11% had congestive heart disease

-6% had coronary artery disease

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- 21% had hypertension
- 3% had hypotension
- 2% had idiopathic/primary electrical disease
- 2% had myocardial infarction-13% had syncope
- 15% had valve dysfunction
- 11% had other cardiovascular history
- 54% had previous cardiovascular surgery
- 10% had atrial fibrillation
- 6% had atrial tachycardia
- 6% had supraventricular tachycardia
- 2% had PVC5% had right bundle branch block

Other diseases

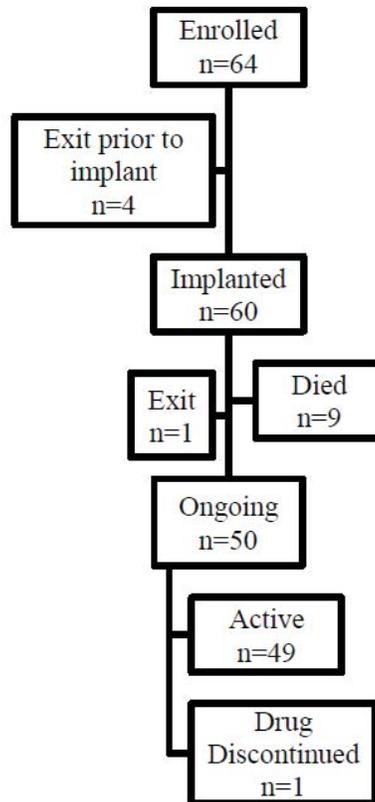
- 11% had diabetes
- 12% had hyperlipidemia
- 6% had hyperthyroidism
- 13% had hypothyroidism
- 6% had renal dysfunction
- 35% had GERD
- 14% had obesity
- 5% had hepatitis
- 6% had DVT
- 19% had peripheral edema
- 18% had Raynaud's phenomenon
- 33% had smoking history
- 22% had sleep apnea
- 11% had asthma
- 11% had pneumonia
- 10% had scleroderma
- 10% had SLE
- 8% had RA

6.2.2 Subject Disposition

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 successful implants with RIS. The first subject was enrolled on June 14, 2011, and the final subject was enrolled on November 20, 2012. There were four subjects who left the study prior to receiving the implant. These are shown below. The reasons, including the two infections, are plausible reasons for not receiving the implant.

Figure 2. Subject Disposition

Figure 10-1. Subject Disposition



Deaths: There have been nine deaths post-implant. These deaths are shown below.

Table 5. Subject Deaths**Table 12-17. Subject Deaths**

Subject	Days After First Implant	Cause of Death (Preferred Term)
(b) (6)	87	Cardiac failure
	129	Pulmonary embolism
	299	Right ventricular failure
	615	Cardiac failure
	728	Cardiopulmonary failure
	857	Cardiac arrest
	888	Respiratory failure
	995	Haemoptysis
	1139	Pulmonary arterial hypertension

Source: IndividualAdverseEvents.sas

6.2.3 Analysis of Primary Endpoint(s)

The endpoint of this objective was catheter-related complications per 1000 subject days. Results for this endpoint at that time are shown below (cut-off date of June 21, 2013). The subjects had 0.27 catheter related complications per 1000 days of use.

Table 6. Primary Objective**Table 34 Primary Objective: Catheter-Related Complications at the Pre-specified Analysis Point**

Performance Goal	Patient Days	Catheter-related Complications	Catheter-related Complications Per 1000 Days	One-sided upper 97.5% confidence bound	P-value
Rate per 1000 days < 2.5	22,013	6	0.27	0.59	<0.0001

An update includes data through July 24, 2014. Of the 60 implanted subjects, there were 44,085 subject days of follow-up (range 87 - 1088 days per subject). These updated results are shown below. The subjects had 0.16 catheter related complications per 1000 days of use.

Table 7. Primary Objective (updated)

Table 35 Primary Objective: Catheter-Related Complications - Updated

Performance Goal	Patient Days	Catheter-related Complications	Catheter-related Complications Per 1000 Days	One-sided upper 97.5% confidence bound
Rate per 1000 days < 2.5	44,085	7	0.16	0.33

There were a total of 7 catheter-related complications (in four subjects) over the course of the study (note, as pre-specified, this includes one procedure-related pneumothorax classified as a complication). These complications reported by 4 subjects are shown below.

Table 8. Primary Endpoint Events

Table 36 Primary Endpoint Events

Subject ID	Days post-implant	Preferred Term	AE Description
(b) (6)	0	Pneumothorax	It was noted that the surgeon had venous access difficulty during the implant procedure. Following the procedure the subject got up to go to the bathroom and reported shortness of breath. A chest x-ray showed a large left pneumothorax. A chest tube was inserted.
	7	Device dislocation	On (b) (6) the subject hyperextended her arm. The catheter slid into the intraclavicular region and the subject reported pain, erythema and swelling at the catheter insertion site (left clavicle), left neck, and left shoulder. She also reported pain radiating down her left arm. System modification performed on (b) (6)
	42	Device dislocation	On (b) (6) the subject complained of non-radiating stabbing pain in her left abdomen above the implanted pump, which was exacerbated with movement or sitting up. It was noted that the left abdomen was swollen above the implanted pump. The subject's left upper quadrant was tender with palpation. Abdominal CT scan showed pump and catheter in subcutaneous tissue of left abdomen. Admitted to hospital on (b) (6) System modification done on (b) (6)

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Subject ID	Days post-implant	Preferred Term	AE Description
(b) (6)	22	Device dislocation	On (b) (6) the subject's recliner chair broke and caused her to fall backwards. She did not have any assistance and pulled / strained herself trying to get out of her chair. On (b) (6) she contacted the site and complained of muscle soreness and fatigue. On (b) (6) the site contacted the subject and she reported abdominal soreness and noted that the area near the pump had "a little redness". The subject refused to come in to be seen. On (b) (6) the site contacted the subject and she stated that the redness was worse. She noted that it "had spider web and a lightning streak above her pump site". The subject was advised to come in for assessment. On (b) (6) fluoroscopy was used to image pump and catheter. The catheter was found completely in the abdominal pocket.
	338	Device damage	On (b) (6) the subject reported soreness and inflammation at pump site (lower right abdomen) that had decreased but persisted for two weeks. The subject's last refill was on (b) (6) and the subject denied any fever, discharge, heat from site, or worsening of PAH symptoms. Fluoroscopy was utilized to image pump system integrity and the PI believed the system was intact. In August the subject was evaluated by Dermatology and Infectious Disease. On (b) (6) the subject's pump/catheter was explanted due to possible catheter leak and site pain. A new system was implanted on the left side with no complications. The explanted catheter was found to have been damaged (punctured).
	1021	Device damage	On (b) (6) the subject had a difficult refill. After three attempts were made, some redness was noted. After two additional attempts, the redness appeared to spread. At that time, fluoroscopy was requested and the catheter appeared to be in front of pump. The site accessed the pump under fluoro & completed the refill. The subject denied any worsening PAH symptoms including SOB, dyspnea, headache, flushing or chest pain. Following the refill, no systemic symptoms were reported but the subject continued to have site pain and redness. On (b) (6) the subject's pump/catheter was explanted due to possible catheter leak and site pain. A new system was implanted on the left side with no complications. The explanted catheter was found to have been damaged (punctured).
(b) (6)	187	Venous stenosis	On (b) (6) the subject notified the coordinator of a new onset of right upper extremity edema, which began in the right hand on the evening of (b) (6). By the morning of (b) (6) it had extended to the upper arm. On the afternoon of (b) (6) the subject saw her PCP for a regularly scheduled apt. The PCP ordered venous doppler studies, which were completed on (b) (6), and were interpreted as negative. On (b) (6) the subject called the study coordinator to report the edema was worsening. She also now reported some pain with the increased swelling and noted intermittent temperature and color changes in fingers of right hand. The subject was brought to clinic for evaluation and admitted to the hospital for further workup. The final diagnosis was "Stenosis at the junction of the right subclavian vein-SVC".

Table 37 Catheter-Related Observations

Subject ID	Days post-implant	Preferred Term	AE Description
(b) (6)	0	Pneumothorax	Following the implant procedure the subject was transferred to the PACU where she was noted to be dyspneic (oxygen saturations in the 80s), hypotensive (SBP in the 80s), and in severe pain. A chest x-ray was obtained and a modest right pneumothorax was seen. The subject was treated with supplemental oxygen (100% non-rebreather mask), fluid bolus, and IV Dilaudid for pain.

There were two reports of pneumothorax, 3 reports of device dislocation, 2 reports of device damage, 1 report of venous stasis.

6.1.5 Analysis of Secondary Endpoints(s)

6-Minute Walk Test

The table below shows the change in walk distance is shown below.

Table 9. Six-Minute Walk Test**Table 39 Change in Six-minute Walk from Baseline to 6 Weeks**

	Six-minute Walk
Baseline	
n recorded	60
Mean ± Standard Deviation (m)	423 ± 99
Median (m)	422
Range (m)	134 – 637
6 Weeks	
n recorded	58
Mean ± Standard Deviation (m)	422 ± 118
Median (m)	428
Range (m)	0 – 675
Absolute Change at 6 Weeks	
n recorded	58
Mean ± Standard Deviation (m)	-2.4 ± 86.5
95% confidence interval (m)	-25.2 – 20.3
Median (m)	7.0
Range (m)	-521 – 139
Percent Change at 6 Weeks	
n recorded	58
Mean ± Standard Deviation (%)	0.2 ± 19.3
95% confidence interval (%)	-4.9 – 5.2
Median (%)	1.5
Range (%)	-100 – 33

The mean percentage increase in six-minute walk in the first six weeks post-implant was 0.2%. This result is included for completeness. Its validity is questioned because of the study's uncontrolled design. The drug's dose was unchanged with pump implantation so no change in walk distance was expected.

Quality of Life

Scores were calculated using the methods in the CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review) Guidelines for Users. If four or more responses in the Activity section were missing, then the Activity Scale score was missing for that subject and visit. Similar rules applied if six or more responses are missing for the Symptom and QoL scales.

CAMPHOR results from baseline to six months can be seen below. For this analysis, a subject was considered better or worse if their score changed by at least two points. Change in the three scores was minimal, with the average scores being within two of baseline, and many subjects scoring no change.

Table 10. CAMPHOR Results

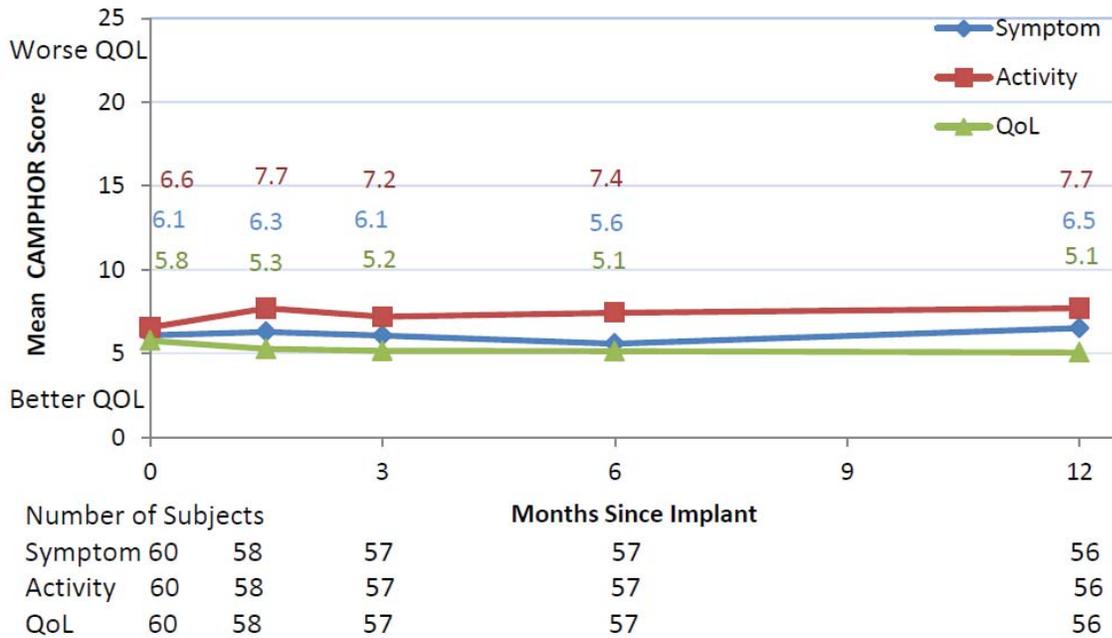
Table 41 CAMPHOR Baseline to Six Months Results

	Symptom Scale	Activity Scale	QoL Scale
Mean Score Change ± S.D.	-0.37 ± 3.51	1.03 ± 3.10	-0.51 ± 3.07
95% Confidence Interval	(-1.30, 0.56)	(0.20, 1.85)	(-1.32, 0.30)
<u>Change</u>			
Better	19 (33%)	10 (18%)	18 (32%)
No Change	24 (42%)	26 (46%)	29 (51%)
Worse	14 (25%)	21 (37%)	10 (18%)

CAMPHOR scores were also collected at six weeks, three months, and twelve months post-implant. Results over time are shown below.

Figure 3. Mean CAMPHOR Scores Over Time

Figure 8 Mean CAMPHOR Score Over Time



The EQ-5D is a self-reported 6-question questionnaire that measures general health-related quality of life on 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is scored on a scale of approximately 0 to 1, with 1 being perfect health.

Of the 60 implanted subjects, all had a baseline EQ-5D summary health index score, and 58 subjects had an EQ-5D summary health index score at six months. The two subjects who did not have a score at six months had died prior to their six month visit. The table below EQ-5D summary health score results from baseline to six month.

Table 11. EQ-5D Results

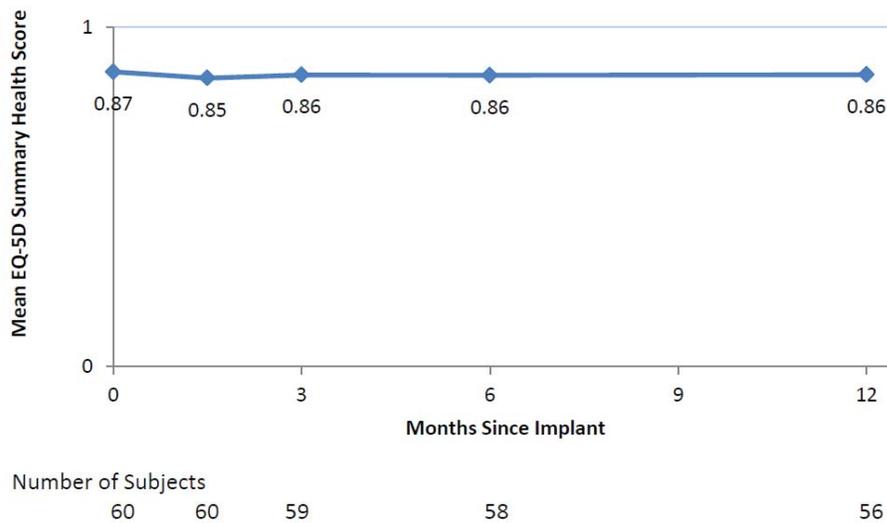
Table 43 EQ-5D Baseline to Six Months Summary Health Score Results

	EQ-5D Summary Health Score
Baseline	
n recorded	60
Mean ± Standard Deviation	0.87 ± 0.13
Median	0.84
Range	0.44 - 1.00
6 Months	
n recorded	58
Mean ± Standard Deviation (m)	0.86 ± 0.15
Median	0.84
Range	0.31 - 1.00
Absolute Change at 6 Months	
n recorded	58
Mean ± Standard Deviation	-0.01 ± 0.10
95% confidence interval	(-0.04, 0.02)
Median	0.00
Range	-0.40 - 0.22

In addition to baseline and six months, EQ-5D was also collected at six weeks, three months, and twelve months. The mean summary score at each time is shown below.

Figure 4. EQ-5D Summary Over Time

Figure 11 Mean EQ-5D Summary Health Score Over Time

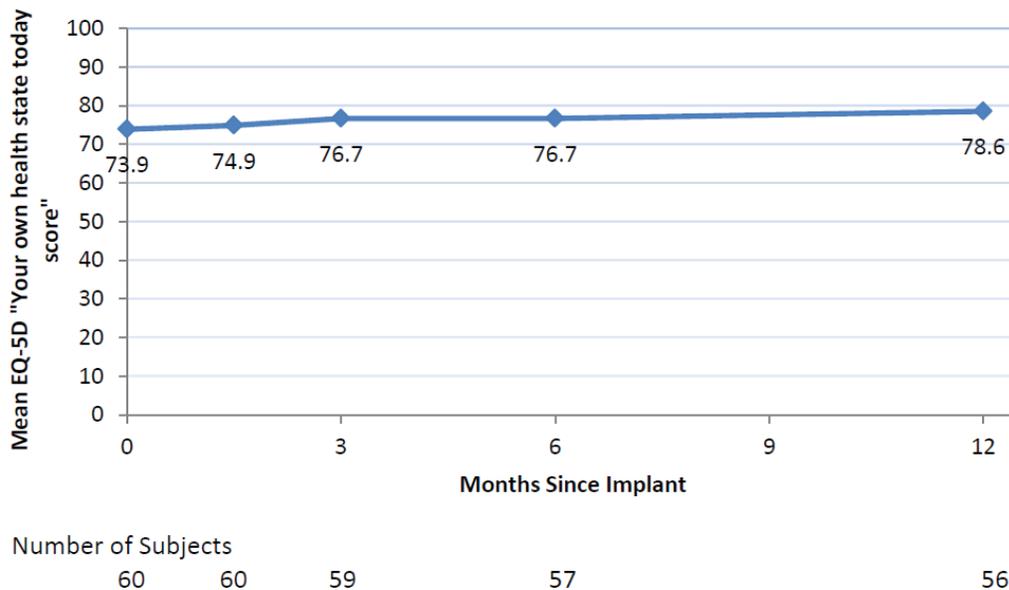


Your Own Health State Today Score

In addition to the questionnaire, the following was asked, “We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.” The subject was then given a visual analog scale measuring from 0-100 to complete. The figure below shows the results.

Figure 5. EQ-5D Visual Analog Scale

Figure 13 EQ-5D Visual Analog Scale



“Your own health state today score” slightly improved over time.

FACIT-TS-G Treatment Satisfaction survey

This survey included eight questions given at six weeks and six months post-implant, prior to the six-minute walk.

At six weeks post-implant, according to the FACIT-TS-G survey, subjects were satisfied with the therapy with a mean treatment satisfaction score of 94.7 (out of 100) and a mean recommendation score of 98.3. For the question “How do you rate this treatment overall?”, at six weeks and at six months all subjects reported good, very good, or excellent. Also, at 6 months, 53% felt the effectiveness of the treatment was better than expected.

Overall, there was little change in quality of life measured by these instruments over 6 months, A not unexpected finding given the progressiveness of the disease.

7 Review of Safety

Safety Summary

The cut-off date for the clinical safety database is 08 January 2016.

The safety data are based on a total of 197 subject-years of documented implanted follow-up time, an average of 3.3 years (range: 87 to 1,625 days) among the 60 implanted subjects. All subjects who were alive at the cut-off date completed their 3-year follow-up visit.

There were nine deaths among the 60 implanted subjects. None of the deaths were related to Remodulin or RIS. The estimated mortality was 5%, 8%, and 13% at 1, 2, and 3 years, respectively. These mortality rates are similar to those reported in the USPI for Tyvaso and Orenitram in uncontrolled long-term studies.

A total of 147 post implant SAEs occurred in 45 of the 60 implanted subjects. The most frequently reported SAEs (>10% subjects) were pneumonia and immediate post-injection reaction. The post-injection reactions included six treprostinil-related events in five subjects during a pump refill, and involved flushing, headache, nausea, and/or hemodynamic changes.

AEs of special interest included device complications, infections, administration site reactions and cardiac disorders. These AEs are summarized below.

- Nineteen (32%) subjects had device complication. There were 6 catheter-related complications and 2 procedure-related pneumothorax complications had occurred. One subject (b) (6) had three of the six catheter-related complications and ultimately had the implanted system explanted as a result of sepsis, pump pocket infection and catheter incision site infection after her third system modification. There were 7 system modifications in 3 subjects whereby the catheter and / or pump required invasive, surgical modification. Six of the system modifications were in two subjects due to catheter dislocation, catheter damage or infection. The seventh system modification involved replacement of the sutureless connector due to suspected leak.
- Fifty-four (90%) subjects had at least 1 administration site reaction. AEs that occurred in >10% subjects included implant site pain (79%), injection site reaction (25%), injection site pain (22%) and implant site bruising (17%). There were two subjects with SAEs: (b) (6) had pain and erythema with an onset of 8 hours post refill and (b) (6) had symptoms of subcutaneous Remodulin exposure within minutes of refill.
- Fifty-four (90%) subjects had at least 1 infection. Common infections were upper respiratory infection (48%), nasopharyngitis (20%), bronchitis (18%), pneumonia (18%), sinusitis (13%), urinary tract infection (12%) and influenza (10%). There were 19 (32%) subjects with SAEs, of which 3 subjects experienced infection-related device complications. (b) (6) had pneumonia legionella resulting in septic shock, (b) (6) had sepsis after she received her initial implant plus three replacements, and (b) (6) had a pump pocket infection.
- There were 27 subjects (45%) with at least 1 cardiac disorder, of which 17 subjects experienced an SAE. Fourteen subjects (23%) had 37 arrhythmic AEs on the day of implant or post-implant, including 27 atrial arrhythmias, 9 ventricular arrhythmias and 1

cardiac arrest. Two of these events (atrial fibrillation and tachycardia) occurred on the day of implant, neither was serious and both resolved within a day of occurrence.

An issue identified during the review was decrease in the delivery accuracy of the pump over time. The accuracy ratio was approximately 0.8 after 3 years. The applicant allowed a 14.5% delivery accuracy plus a 10% measurement error in the actual residual volume. There were 24 (1.3%) measurements that exceeded the pre-specified accuracy threshold. Although no definitive conclusions can be made without a control arm, there was no apparent clinical consequence of the decreased delivery accuracy with time: patients did not have an increase in PAH symptoms and there was no correlation between the accuracy ratio and dose increase.

7.1 Methods

An AEAC was utilized at regular intervals throughout the study to adjudicate all AEs and subject deaths. The AEAC consisted of four non-Medtronic employed physicians in the US representing cardiology/PAH, vascular surgery, and anesthesiology/pain management. None of the AEAC members were DelIVery for PAH clinical investigators. At least three AEAC members adjudicated, at a minimum, all deaths, serious AEs, and AEs related to any component of the system under investigation and/or Remodulin. All other AEs were adjudicated by at least one physician member of the AEAC.

Table 12. AEAC Membership

Table 6-2. AEAC Membership

Member Name	Clinical Specialty / AEAC Role	Contact information
(b) (4)	Cardiology / PAH and AEAC Chairman	(b) (4)
	Cardiology / PAH	
	Vascular Surgery	
	Anesthesiologist / Pain Management	

A Data Monitoring Committee (DMC) was utilized for assessing the accumulating data on safety of the catheter during the study at regular intervals. They were also responsible for safeguarding the interests of study subjects and for monitoring the overall conduct of the clinical study. This independent, multidisciplinary group consisted of three non-Medtronic employed members, representing expertise in PAH, chronically implanted central venous catheters, pacing leads, implanted SynchroMed II pumps and a statistician. No DMC member participated as a DelIVery for PAH clinical investigator, or participated in another committee responsible for trial activities.

Table 6-3. DMC Membership

Member Name	Clinical Specialty / DMC Role	Contact information
(b) (4)	PAH and CVC / pacing lead implanting physician DMC Chair	(b) (4)
	SynchroMed II implanter	
	Statistician	

All AEs were reported throughout the study. 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). Preferred Terms (PT) are used in the summary tables except catheter dislodgement which is a LLT.

Reviewer's analysis of the safety data was performed using MAED where preferred terms for AEs were classified using MedRA 18.1. All plots were generated using R software, version 3.2.2.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Adverse events were collected in a single-arm clinical trial, g100017.

7.1.2 Categorization of Adverse Events

The AEAC will review all adverse events and deaths at regular intervals. The committee will assess, classify and designate a relationship per the definitions in below. Complications and

observation will be assigned for all procedure, system component, treprostinil, drug refill process, and catheter patency test related events only.

Table 13. AE Definitions

Table 77 Adverse Event Definitions

General	
Adverse Event (AE)	Any untoward medical occurrence in a subject <i>NOTE:</i> 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)
Adverse Drug Experience	Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action. (21 CFR 314.80 (a))
Adverse Device Effect (ADE)	Any untoward and unintended response to a medical device. <i>NOTE 1:</i> This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. <i>NOTE 2:</i> This definition includes any event that is a result of a user error. <i>NOTE 3:</i> This definition includes patients and users. (ISO 14155-1:2003(E) 3.1)
Seriousness	
Unanticipated Adverse Device Effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CIP or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3 (s))
Unexpected Adverse Drug Experience	Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product. (21 CFR 314.80 (a))

<p>Serious Adverse Event (SAE)</p>	<p>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)</p>
<p>Serious Adverse Device Effect</p>	<p>An Adverse Device Effect that has resulted in any of the consequences characteristic of a Serious Adverse Event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune. (ISO 14155-1:2003(E) 3.18)</p>
<p>Serious Adverse Drug Experience</p>	<p>Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.</p> <p><i>Disability.</i> A substantial disruption of a person's ability to conduct normal life functions.</p> <p><i>Life-threatening adverse drug experience.</i> Any adverse drug experience that places the patient, in the view of the initial reporter, at <i>immediate</i> risk of death from the adverse drug experience as it occurred, <i>i.e.</i> , it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death. (21 CFR 314.80 (a))</p>
<p>Complication</p>	<p>An adverse event that results in death, involves any termination of significant device function, or requires an invasive intervention</p> <ul style="list-style-type: none"> • Noninvasive: Noninvasive, when applied to a diagnostic device or procedure, means one that does not by design or intention: (1) Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or (2) enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or vagina beyond the cervical os. For purposes of this part, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive. (21 CFR 812.3(k)) <p>NOTE: Pump refills and catheter patency tests are not considered complications.</p>
<p>Observation</p>	<p>Any adverse event that is not a complication</p>

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As of a cut-off date of 08 January 2016, there have been a total of 197 subject-years of documented implanted follow-up time, an average of 3.3 years (range: 87 to 1,625 days) among the 60 implanted subjects.

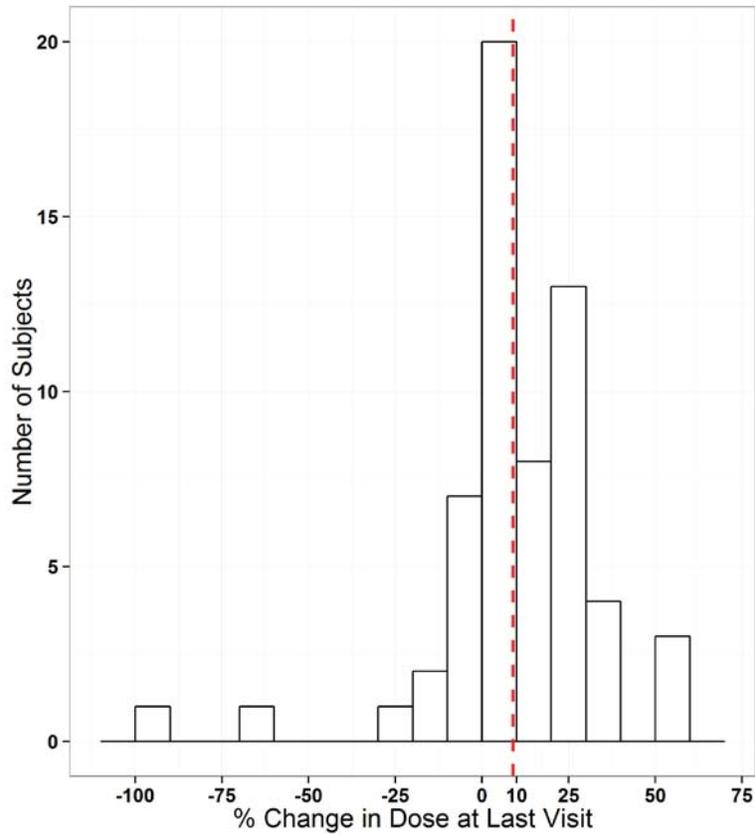
Table 14. Subject Follow-Up

Study Visit	Completed Visit	Discontinued Study	Died
1-week	60	0	0
6-week	60	0	0
3-month	59	0	1
6-month	58	0	2
12-month	57	0	3
18-month	57	0	3
24-month	55	0	5
30-month	53	0	7
36-month	52	0	8
42-month	24	1	9
48-month	10	1	9

Cross-reference Table 12-1 in Summary of Drug-Device Safety Update

The mean Remodulin dose at baseline was 72.2 ± 29.5 ng/kg/min with a range of 22 to 160 ng/kg/min. At the most recent study visit prior to this data freeze, the mean Remodulin dose was 79.8 ± 26.2 ng/kg/min with a range of 26.9 to 142.0 ng/kg/min. The distribution of percent change in dose at the last study visit is shown in Figure below. 38 (63%) subjects were receiving a higher dose than at baseline; however, the mean increase in dose is <10%. The CRF did not capture the reason for dose increases or decreases.

Figure 6. Distribution of Dose Change at the Last Study Visit (cutoff date: 16 Jan 2016)



Reviewer's analysis based on applicant's dataset refill.xpt

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

The table below displays schedule of visits and assessments conducted.

Table 15. Schedule of Events**Table 9-1. Overall Time and Events Schedule**

STUDY PROCEDURE	Baseline	Implant	1 week Follow-up	6 Week, 3, 6, and 12 Month Follow-up	Unscheduled Follow-up	Long-Term Follow-up	Study Exit
Date of Consent and HIPAA / data protection authorization	X						
Inclusion / Exclusion Criteria	X						
Demographics, Medical History Review	X						
Pregnancy screen (if applicable)	X						
Physical Exam	X			X			
NYHA functional classification	X			X			
Subject / caregiver involvement assessment	X			X			
6MWT	X			X			
Quality of Life Assessments	X			X			
Treatment Satisfaction Survey				X (6wk , 6mo only)			
Blood Sample Collection for Basic Metabolic Profile	X						
Catheter Implanter Survey		X					
Pump Fill / Refill Data (if necessary)		X	X	X	X	X	X
Fluoroscopy / Radiograph for Verification of Catheter and Pump Placement		X					
Adverse Events	X	X	X	X	X	X	X
Blood Sample Collection for plasma treprostini level	X		X				
Blood Sample Collection for Plasma treprostini level (if catheter occlusion suspected)							
Device Traceability record updates							
Medications							
Pregnancy Notification							
Device Malfunctions							
System Modifications							
Study Deviations							
Death							

As needed

7.2.5 Metabolic, Clearance, and Interaction Workup

Treprostini is substantially metabolized by the liver, primarily by CYP2C8. Human pharmacokinetic studies with an oral formulation of treprostini (treprostini diethanolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil increases exposure (both C_{max} and AUC) to treprostini. Co-administration of the

CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It has not been determined if the safety and efficacy of treprostinil by the parenteral (subcutaneously or intravenously) route are altered by inhibitors or inducers of CYP2C8

Concomitant administration of Remodulin with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension.

Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among subjects receiving anticoagulants.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Most common AEs (incidence >3%) reported in clinical trials with treprostinil injection are subcutaneous infusion site pain and reaction, headache, diarrhea, nausea, jaw pain, vasodilatation, dizziness, edema, pruritus and hypotension.

7.3 Major Safety Results

7.3.1 Deaths

There were 9 deaths among the 60 implanted subjects. The cause of death for each subject is summarized in the following table. None of the deaths were related to Remodulin or the RIS.

Table 16. Summary of Deaths

Subject	Summary of Death
(b) (6)	63 year old female with history of pulmonary hypertension, congestive heart failure, syncope of unknown etiology, gastroesophageal reflux disease, sleep apnea (with CPAP), asthma, fibromyalgia, thrombocytopenia, epistaxis and smoking history. Subject was NYHA Class III at Baseline. Subject had a successful implant of the DelIVery for PAH system on (b) (6). Subject was admitted on (b) (6) for decompensated heart failure and pancytopenia. Date of death was (b) (6)
(b) (6)	49 year old female with history of pulmonary hypertension, hyperthyroidism, hypothyroidism, GERD, borderline sleep apnea, previous smoking history, multiple miscarriages (6 or 7), antiphospholipid disease, glaucoma, migraine headaches, and autoimmune hemolytic anemia. Subject was NYHA Class III at Baseline. Subject had a successful implant of the DelIVery for PAH system on (b) (6). Subject died from cardiopulmonary arrest related to right heart failure with severe iatrogenic volume overload. Date of death was (b) (6).
(b) (6)	62 year old male with history of pulmonary hypertension, atrial flutter, varicose veins, untreated sleep apnea, and hypoxia. Subject was NYHA Class II at Baseline. Subject had a successful implant of the DelIVery for PAH system on (b) (6). Subject died from right heart failure progression of underlying disease on (b) (6).

<i>Subject</i>	<i>Summary of Death</i>
(b) (6)	63 year old male with history of pulmonary hypertension, mitral and tricuspid valve dysfunction, left ventricular hypertrophy, raynaud's phenomenon, pneumonia, (past) smoking, hypoxia, empyema, rheumatoid arthritis, antisynthetase syndrome, dyslipidemia, dysphagia, and kidney stone surgery. Subject was NYHA Class II at Baseline. Subject had a successful implant of the DelIVery for PAH system on (b) (6). Subject died from respiratory failure secondary to interstitial lung disease, COPD exacerbation, progression of severe pulmonary hypertension and pneumonia. Date of death was (b) (6).
	44 year old female with history of pulmonary hypertension and gastritis with no other applicable medical history reported. Subject was NYHA Class II at Baseline. Subject had a successful implant of the DelIVery for PAH system on (b) (6). Subject was involved in a motor vehicle accident on (b) (6) sustaining cervical strain and later developed lower leg pain. Date of death was (b) (6). Autopsy report stated the cause of death was pulmonary embolism of 3.5cm that occluded the pulmonary trunk. Lower extremities were not examined during the autopsy.
	75 year old male with history of pulmonary hypertension, pulmonary embolism, asthma, rheumatoid arthritis, nasal congestion, post-nasal drip, generalized pruritus, alopecia, and loss of finger and toe nails. Subject was NYHA Class I at Baseline. Subject had a successful implant of the DelIVery for PAH system on (b) (6). the subject was hospitalized with increased dyspnea, volume overload, bilateral pitting edema on his lower extremities, and hypotension. Subject died from respiratory failure and right heart failure on (b) (6).
	43 year old female with history of pulmonary hypertension, hypotension, primary/idiopathic electrical disease, syncope (vasovagal), atrial fibrillation (permanent), atrial flutter, atrial tachycardia, renal dysfunction (not requiring dialysis), obesity, peripheral edema, sleep apnea, persistent cough, pneumonia, asthma, and subject was a past smoker, Subject was NYHA Class II at Baseline. Subject had a successful implant of the DelIVery for PAH system on (b) (6). Subject died from cardiac arrest on (b) (6).
	69 year old male with history of Hypertension, Pulmonary hypertension (PH), tricuspid valve dysfunction, Sinus Tachycardia, type II diabetes, Gastroesophageal disease, hiatal hernia, obesity, peripheral edema, sleep apnea treated by CPAP, pulmonary fibrosis, Rheumatoid arthritis, Depression, Insomnia, and Right Ventricular Failure. Subject was NYHA Class III at Baseline. Subject had a successful implant of the DelIVery for PAH system on (b) (6). The subject was admitted to the hospital on (b) (6) with acute decompensated right heart failure. The subject died from pulmonary hypertension on (b) (6).
	26 year old male with history of congenital heart disease, PAH, Eisenmenger's Syndrome secondary Ventricular Septal Defect, Great vessel switch procedure done at 2 days of age (b) (6), Supraventricular tachycardia, Cerebrovascular accident (stroke), "Hypoxia- O2 sat 91-92%", migraine headaches, macular erythema rash right arm. Subject was NYHA Class III at Baseline. Subject had a successful implant of the DelIVery for PAH system on (b) (6). Subject has history of

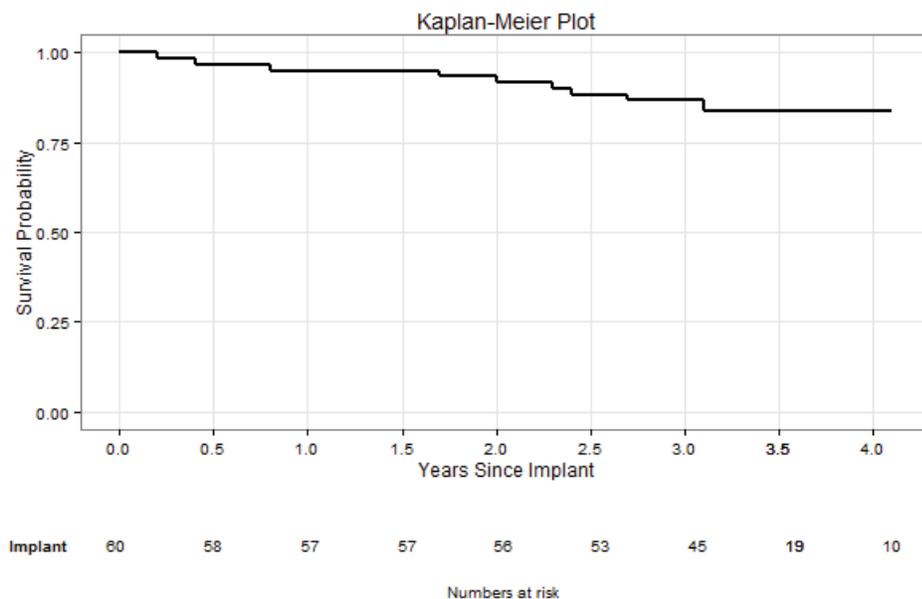
Subject	Summary of Death
	numerous hemoptysis AEs throughout the course of the study. The subject was hospitalized from (b) (6) for hemoptysis. The subject died from recurrent massive hemoptysis due to pulmonary vascular bleed on (b) (6).

Reviewer’s table based on Death Narratives (section 12.3.2.1 in Summary of Device-Drug Safety Update)

A Kaplan-Meier plot shows the survival probability, where Time 0 was the day of implant, and subjects were censored on the date of their last follow-up. The estimated mortality was 5%, 8%, and 13% at 1, 2, and 3 years, respectively.

Reviewer’s comment: Mortality rates in this trial appear in the same range to the rates reported in uncontrolled long-term trials of treprostinil. Per the Tyvaso label, the Kaplan-Meier estimates of survival at 1, 2, and 3 years were 97%, 91% and 82%, respectively, in the open-label extension to the pivotal trial. Per the Orenitram label, survival was 92%, 87% and 82% at the end of 1, 2, and 3 years.

Figure 7. Kaplan-Meier Plot of Survival



Reviewer’s analysis based on Applicant’s dataset anal-fu.xpt

7.3.2 Serious Adverse Events

A total of 146 SAEs occurred post-implant in 45 of the 60 implanted subjects (75%). Additionally, one SAE (pneumothorax) occurred during implant, and 5 SAEs occurred pre-implant, including 4 infections (3 temporary line-related and one Klebsiella Bacteremia) and one case of atrial flutter. Two of the subjects with serious pre-implant infections were not implanted.

SAEs grouped by MedDRA System Organ Class (SOC) that occurred in >10% of subjects were infections (31.7%), cardiac disorders (28%), administration site conditions (22%), respiratory disorders (22%), and vascular disorders (10%).

Table 17. Listing of Serious Adverse Events by MedDRA Preferred Term (>1 Subject)

Preferred Term	Number Events (N=152)	Subjects (N=60)	
Pneumonia	10	8	13.30%
Immediate post-injection reaction	9	7	11.70%
Atrial fibrillation	9	4	6.70%
Cardiac failure	4	4	6.70%
Fluid overload	5	4	6.70%
Chest pain	3	3	5%
Pneumothorax	3	3	5%
Right ventricular failure	4	3	5%
Atrial flutter	4	2	3.3%
Atrial tachycardia	2	2	3.3%
Bronchitis	2	2	3.3%
Clostridium difficile colitis	2	2	3.3%
Device related infection	3	2	3.3%
Dyspnea	2	2	3.3%
Hypotension	3	2	3.3%
Injection site reaction	2	2	3.3%
Lead dislodgement	3	2	3.3%
Pericardial effusion	2	2	3.3%
Pulmonary arterial hypertension	2	2	3.3%
Supraventricular tachycardia	2	2	3.3%
Syncope	2	2	3.3%

Reviewer's analysis based on Applicant's dataset adae.xpt

7.3.3 Dropouts and/or Discontinuations

Four subjects exited the study prior to implant (two developed external line infections, one clinically worsened, and one was too small to accept the implantable pump bulk and weight).

One subject had discontinued therapy due to AEs. Subject (b) (6) was a 64 year old female who had a successful implantation on (b) (6). The subject had four complications.

1. Catheter had dislodged and had migrated into the pump pocket after reporting falling out of recliner. The subject had a revision surgery on (b) (6) during which both the pump and catheter were replaced. During the revision, the anchoring sleeve was not found with the catheter in the pump pocket. The adverse event was classified as serious and catheter related and has been adjudicated by the AEAC.
2. On (b) (6) the site performed a system modification (pump and catheter) due to suspected local delivery of Remodulin in the pump pocket. New system was placed on the left. Analysis on the explanted catheter showed that it had been punctured during the refill process. Follow-up on (b) (6) indicated that the subject's pain was improving and there was no site infection or fever. On (b) (6), the AEAC adjudicated the event as serious, catheter related, Remodulin related, as well as refill process related.
3. On (b) (6) the subject's pump / catheter was explanted due to possible catheter leak and site pain. A new system was implanted on the left side with no complications. The site reported that the erythema and soreness resolved on (b) (6). Analysis on the explanted catheter showed that it had been punctured during the refill process. On (b) (6), the AEAC adjudicated the event as serious, catheter related, Remodulin related, as well as refill process related.
4. On (b) (6), following the system modification that this subject had on (b) (6), the subject reported pain at the pump site and in the left shoulder. The subject's temperature was 102. Upon exam the subject was hypoxic and both of the incision sites appeared inflamed and fluctuant. The subject was admitted to the hospital on (b) (6) with a diagnosis of sepsis and a full system explant was performed on (b) (6). No new system was implanted. Analysis on the explanted pump and catheter showed no functional or significant anomalies. On (b) (6), the AEAC adjudicated the event as serious and system modification related. The subject was discontinued from the study after the device was explanted and not replaced due to pump pocket infection, catheter incision site infection and sepsis. The subject exited the study since she no longer had the study system and there were no plans for re-implantation.

7.3.4 Adverse Events of Special Interest

RIS Complications

Complications are defined as AEs that result in death, involves termination of significant device function or requires invasive intervention. There were 19 (32%) subjects with complications and 15 (25%) experienced an SAE. The most common complications are immediate post-injection reaction (10% subjects) and implant site extravasation (7% of subjects).

Complications include the 3 subjects (b) (6) who experienced 6 catheter-related complications and 1 subject (b) (6) who experienced a procedure-related pneumothorax. The description of these complications was previously provided.

A system modification is any event whereby the catheter and/or pump required invasive modification (*i.e.*, pump or catheter explant, replacement, repositioning). There were 7 system modifications in 3 subjects:

- (b) (6) experienced 2 catheter dislocations on days 11 and 49. In both cases the catheter was explanted and replaced.
- (b) (6) experienced 4 complications related to catheter dislocation, possible leak in catheter and catheter site infection. The pump and catheter were explanted and replaced on 3 occasions, and removed on the fourth occasion.
- (b) (6) had a suspected leak in the sutureless connector. The pump was repositioned.

Table 18. Summary of Complications

	Number Subjects	% Subjects
AEs	19	31.7
SAEs	15	25
Related to Implant Procedure	9	15
Related to Catheter Model 10642	3	5
Related to Remodulin Injection	11	18.3
Related to Refill Procedure	9	15

Reviewer's analysis of Applicant's dataset anal-ae.xpt

Table 19. Adverse Events Considered Complications

MedDRA Preferred Term	Number Events	Number Subjects	% Subjects
Immediate post-injection reaction	8	6	10%
Implant site extravasation	4	4	6.7%
Injection site reaction	3	2	3.3%
Lead dislodgement¹	3	2	3.3%
Atrial fibrillation	2	1	1.7%
Deep vein thrombosis	1	1	1.7%
Device damage¹	2	1	1.7%
Hypotension	1	1	1.7%
Implant site infection	1	1	1.7%
Pneumonia legionella	1	1	1.7%
Pneumothorax¹	1	1	1.7%
Postoperative fever	1	1	1.7%
Renal failure	1	1	1.7%
Sepsis	1	1	1.7%

Septic shock	1	1	1.7%
Urinary retention	1	1	1.7%
<i>Venous stenosis¹</i>	<i>1</i>	<i>1</i>	<i>1.7%</i>
Ventricular tachycardia	1	1	1.7%
Vomiting	1	1	1.7%

Reviewer's analysis of Applicant's dataset anal-ae.xpt Note: 1=indicates catheter-related or procedure-related complications that contributed to the primary safety endpoint. Cross-reference Table 12.21 in Summary of Drug-Device Safety Update.

Administration Site Reactions

There were 54 (90%) subjects with AEs related to MedDRA HLG T administration site reactions and 2 (3%) subjects had a SAE. Five subject's AEs were considered to be complications.

- (b) (6): During refill procedure, blood-tinged fluid (mild seroma) was aspirated from abdomen above access port of Synchroned II pump.
- (b) (6): Pain and Erythema with onset 8 hours post refill. Subject did not report any symptoms before, during, or after refill until pain & erythema was reported 8 hours post refill. The subject was hospitalized for less than 24 hours. Chest x-ray was normal and there was no indication that the pump catheter was misplaced. The AEs were considered serious and related to the Remodulin injection and refill process.
- (b) (6): Subject began having symptoms of subcutaneous Remodulin exposure within minutes following a pump refill procedure. Symptoms included overall body flushing, stomach cramps, nausea and tachycardia. Blood pressure remained stable throughout event. Erythema and pain were noted at the injection site. Subject transferred to the Emergency Department where she reported one episode of "stabbing chest pain", and headache. She also complained of pain that tracked along the catheter site laterally. Erythema and warmth was noted along this track also. The pump dosage was decreased 20% initially, and then was incrementally increased returning the pump to original settings. Stomach cramps, nausea, tachycardia, erythema and pain at injection site, chest pain, and headache all resolved. Subject continued to have flushing. AEs were considered to be serious and related to the Remodulin injection and refill process.
- (b) (6): Subject had seroma noted in pump pocket site after refill.
- (b) (6): Subject had seroma noted in pump pocket site after refill.

The majority of the AEs were classified as related to the implant or refill procedure. The most common AEs are as follows: implant site pain (78%), injection site reaction (25%), Injection site pain (22%), and implant site bruising (16%).

Table 20. Summary of Adverse Events Related to Administration Site Reactions

SOC: Infections and Infestations	Number Subjects	% Subjects
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AEs	54	90
SAEs	2	3.3
Complication	5	8.3
Related to Implant Procedure	47	78.3
<i>Related to Catheter Model 10642</i>	0	0
Related to Remodulin Injection	22	36.7
Related to Refill Procedure	24	40

Reviewer's analysis of Applicant's dataset anal-ae.xpt

Table 21. Adverse Events Related to MedDRA High Level Group Term Administration Site Reactions (>1 Subject)

MedDRA Preferred Term	Number Events	Number Subjects	% Subjects
Implant site pain	49	47	78.3%
Injection site reaction	21	15	25%
Injection site pain	17	13	21.7%
Implant site bruising	10	10	16.7%
Implant site extravasation	4	4	6.7%
Vessel puncture site pain	5	4	6.7%
Implant site swelling	3	3	5%
Implant site erythema	2	2	3.3%
Implant site rash	2	2	3.3%
Injection site discomfort	4	2	3.3%
Injection site erythema	2	2	3.3%

Reviewer's analysis of Applicant's dataset anal-ae.xpt

Infections

Infections were considered an AE of special interest because of the potential risk of infection related to procedures for an implantable system . There were 54 (90%) subjects with AEs related to MedDRA SOC infection and infestation and 19 (32%) subjects had a SAE. In three subjects, infections were considered to be a complication.

- Subject (b) (6) had pneumonia legionella resulting in septic shock which was considered related to the implant procedure based on the timing of the event relative to the procedure, and not due to a specific association.

- Subject (b) (6) developed sepsis after she received her initial implant plus three replacement systems. The device was explanted and the subject withdrew from study (see section 7.3.3. for more details).
- Subject (b) (6) had a pump pocket infection which resolved after this subject had a system modification to replace the sutureless connector.

The most common infections observed in this study are as follows: upper respiratory tract infection (48%), nasopharyngitis (20%), bronchitis (18%), pneumonia (18%), sinusitis (13%), urinary tract infection (11%), and influenza (10%).

Table 22. Summary of Infection Related Adverse Events

SOC: Infections and Infestations	Number Subjects	% Subjects
AEs	54	90
SAEs	19	31.7
Complication	3	5
Related to Implant Procedure	3	5
<i>Related to Catheter Model 10642</i>	0	0
Related to Remodulin Injection	0	0
Related to Refill Procedure	0	0

Reviewer's analysis of Applicant's dataset anal-ae.xpt

Table 23. Adverse Events Related to MedDRA SOC Infection and Infestation (>1 Subject)

MedDRA Preferred Term	Number Events	Number Subjects	% Subjects
Upper respiratory tract infection	53	29	48.3%
Nasopharyngitis	17	12	20%
Bronchitis	11	11	18.3%
Pneumonia	13	11	18.3%
Sinusitis	11	8	13.3%
Urinary tract infection	12	7	11.7%
Influenza	7	6	10%
Ear infection	3	3	5%
Cellulitis	2	2	3.3%
Clostridium difficile colitis	2	2	3.3%

Clinical Review

Reviewers: M Gordon, C Garnett

NDA#208276

Device related infection	3	2	3.3%
Gastroenteritis	2	2	3.3%
Lower respiratory tract infection	2	2	3.3%
Onychomycosis	2	2	3.3%
Tooth infection	3	2	3.3%

Reviewer's analysis of Applicant's dataset anal-ae.xpt

Cardiac Disorders

Cardiac disorders are considered an AE of special interest because cardiac arrhythmias are important contributors to morbidity and mortality in patients with PAH. There were 27 subjects (45%) with at least 1 cardiac disorder, of which 17 subjects experienced an SAE. The most common cardiac disorders were atrial fibrillation (10%), palpitations (10%), right ventricular failure (10%), tachycardia (8%) and cardiac failure (7%).

Fourteen subjects (23%) had 37 arrhythmic AEs on the day of implant or post-implant, including 27 atrial arrhythmias, 9 ventricular arrhythmias and 1 cardiac arrest. Two of these events (atrial fibrillation and tachycardia) occurred on the day of implant– neither was serious and both resolved within a day of occurrence.

One subject (b) (6) reported 14 arrhythmic events. This subject had a medical history of Atrial fibrillation, paroxysmal; premature atrial complexes; ectopic atrial rhythm; premature ventricular complexes; and AV junctional rhythm. The subject was cardioverted many times and underwent cardiac ablation 3.3 y post implant.

Table 24. Summary of Cardiac-Related Adverse Events

SOC: Cardiac Disorders	Number Subjects	% Subjects
AEs	27	45.0
SAEs	17	28.3
Complication	1	1.7
Related to Implant Procedure	2	3.3
<i>Related to Catheter Model 10642</i>	0	0.0
Related to Remodulin Injection	2	3.3
Related to Refill Procedure	1	1.7

Reviewer's analysis of Applicant's dataset anal-ae.xpt

Table 25. Adverse Events Related to MedDRA SOC Cardiac Disorders (>1 Subject)

MedDRA Preferred Term	Number Events	Number Subjects	% Subjects
Atrial fibrillation	18	6	10.0%
Palpitations	9	6	10.0%
Right ventricular failure	7	6	10.0%
Tachycardia	5	5	8.3%
Cardiac failure	5	4	6.7%
Atrial flutter	5	3	5.0%
Pericardial effusion	3	3	5.0%
Atrial tachycardia	2	2	3.3%
Supraventricular tachycardia	2	2	3.3%
Ventricular extrasystoles	2	2	3.3%
Ventricular tachycardia	2	2	3.3%

Reviewer's analysis of Applicant's dataset anal-ae.xpt

Reviewer's comment: Cardiac arrhythmias are not reported as AEs in either the Tyvaso or Remodulin USPIs. In the selexipag clinical trial which followed subjects for an average of 1.4 years, 21% subjects taking selexipag and 22% subjects taking placebo experienced cardiac arrhythmias. Therefore, the incidence of cardiac arrhythmias observed post-implant is expected in this patient population.

7.3.5 Submission Specific Primary Safety Concerns

Catheter-related complications included catheter-related systemic bloodstream infections, site infections, and complications from catheter thrombosis, mechanical dysfunction, and catheter dislocation. Procedure-related pneumothorax complications also counted toward the primary objective. As the primary endpoint of the study, these AEs are described above in efficacy section.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common post-implant AEs were implant site pain, upper respiratory tract infection, worsening PAH, dyspnea, injection site reaction (local symptoms at or around the refill site and may include pain, erythema, and / or swelling), headache, nausea, fatigue, injection site pain, dizziness, hypotension and immediate post-injection reaction (systemic symptoms after refilling the pump including flushing, headache, nausea, and/or hemodynamic changes).

Table 26. Common AEs Occurring in >10% Subjects

<i>MedDRA Preferred Term</i>	<i>Implant (N = 60)</i>				
	<i>Events</i>	<i>Number of subjects</i>	<i>Proportion (%)</i>	<i>Proportion C.I. (lower bound) (%)</i>	<i>Proportion C.I. (upper bound) (%)</i>
Implant site pain	49	47	78.3	66.4	86.9
Upper respiratory tract infection	53	29	48.3	36.2	60.7
Pulmonary arterial hypertension	35	20	33.3	22.7	45.9
Dyspnea	26	18	30.0	19.9	42.5
Headache	22	16	26.7	17.1	39.0
Nausea	16	16	26.7	17.1	39.0
Hypotension	17	15	25.0	15.8	37.2
Injection site reaction	21	15	25.0	15.8	37.2
Fatigue	15	14	23.3	14.4	35.4
Dizziness	16	13	21.7	13.1	33.6
Injection site pain	17	13	21.7	13.1	33.6
Immediate post-injection reaction	16	12	20.0	11.8	31.8
Nasopharyngitis	17	12	20.0	11.8	31.8
Pain in extremity	12	12	20.0	11.8	31.8
Bronchitis	11	11	18.3	10.6	29.9
Pneumonia	13	11	18.3	10.6	29.9
Implant site bruising	10	10	16.7	9.3	28.0
Abdominal pain	9	9	15.0	8.1	26.1
Diarrhoea	10	9	15.0	8.1	26.1
Flushing	9	9	15.0	8.1	26.1
Vomiting	9	9	15.0	8.1	26.1
Anxiety	9	8	13.3	6.9	24.2
Back pain	8	8	13.3	6.9	24.2
Fluid overload	17	8	13.3	6.9	24.2
Sinusitis	11	8	13.3	6.9	24.2
Dyspnoea exertional	9	7	11.7	5.8	22.2
Hypokalaemia	10	7	11.7	5.8	22.2
Musculoskeletal pain	8	7	11.7	5.8	22.2
Urinary tract infection	12	7	11.7	5.8	22.2
Atrial fibrillation	18	6	10.0	4.7	20.2
Influenza	7	6	10.0	4.7	20.2
Insomnia	7	6	10.0	4.7	20.2
Oedema peripheral	8	6	10.0	4.7	20.2

<i>MedDRA Preferred Term</i>	<i>Implant (N = 60)</i>				
	<i>Events</i>	<i>Number of subjects</i>	<i>Proportion (%)</i>	<i>Proportion C.I. (lower bound) (%)</i>	<i>Proportion C.I. (upper bound) (%)</i>
Palpitations	9	6	10.0	4.7	20.2
Right ventricular failure	7	6	10.0	4.7	20.2
Syncope	7	6	10.0	4.7	20.2

Reviewer's MAED analysis using Applicant's datasets anal-ae.xpt and anal-enr.xpt

7.4.2 Laboratory Findings

Clinical laboratory evaluation was not conducted for the study other than as AEs as necessary.

7.4.3 Vital Signs

Vital signs were not collected for the study other than as AEs as necessary.

7.4.4 Electrocardiograms (ECGs)

ECGs were not collected other than as AEs as necessary.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

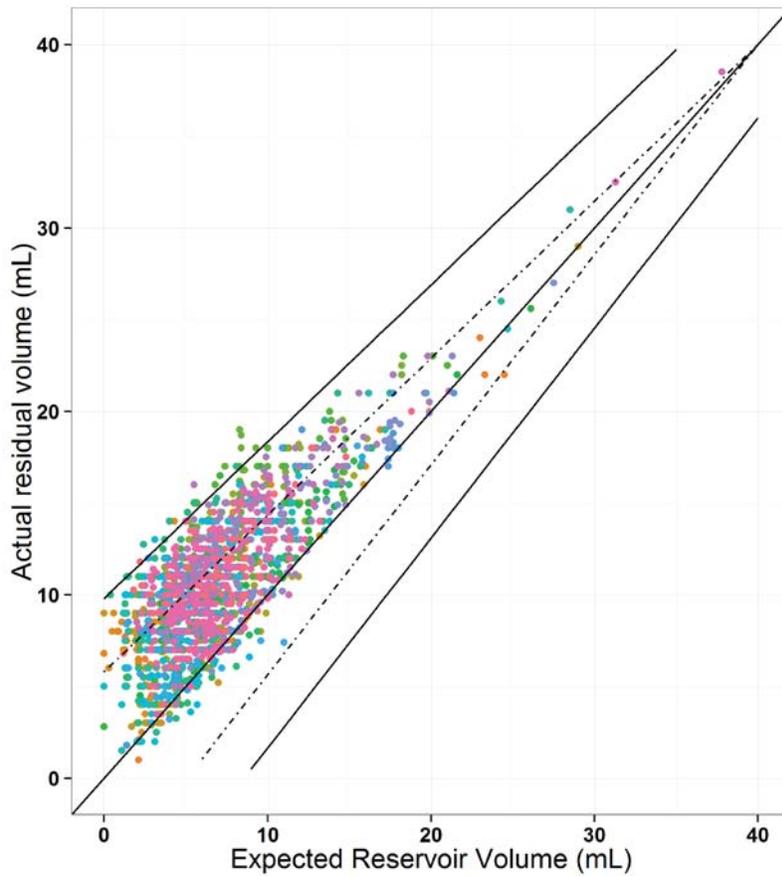
Not applicable.

7.5 Other Safety Explorations

Each time the pump was refilled with Remodulin, the total observed volume dispensed was compared with the total expected (calculated) volume dispensed to compute an accuracy ratio. The pump fluid delivery accuracy data have been reported during 1,781 of the 1,798 refills among 61 pumps in 60 subjects.

The applicant allowed a 14.5% delivery accuracy plus a 10% measurement error in the actual residual volume. There were 24 (1.3%) measurements that exceeded the pre-specified accuracy threshold as shown in figure below.

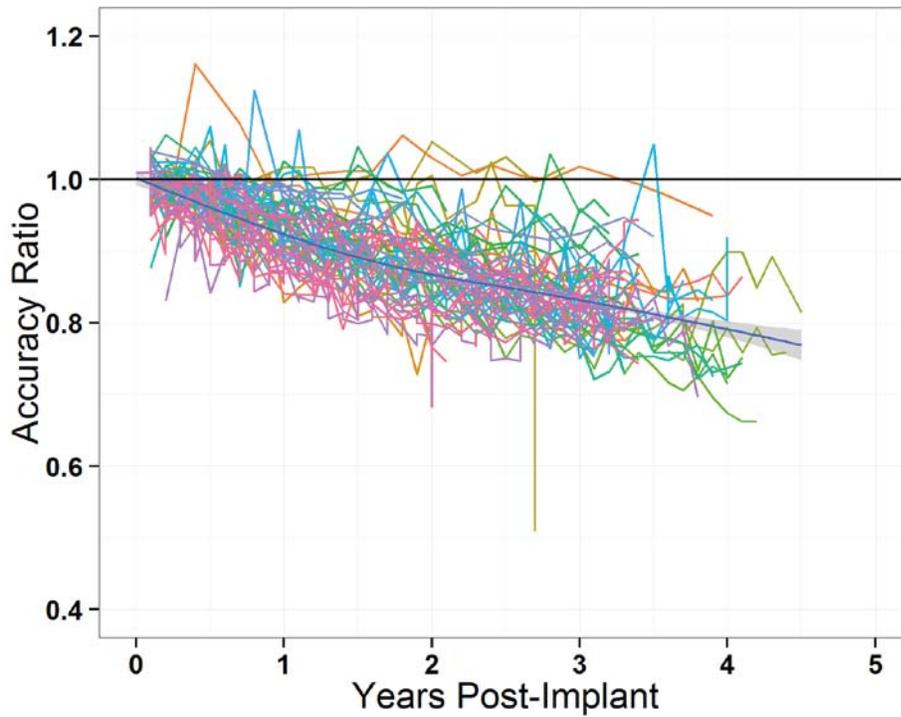
Figure 8. Expected vs. Actual Reservoir Volume



Reviewer's analysis based on Applicant's dataset refill.xpt. Note: Closed circles are observed data; center solid line is the line of unity; dashed lines show $\pm 14.5\%$ delivery accuracy of the pump; and outer solid lines show additional 10% measurement error.

The following figure shows that the Accuracy Ratio decreases over time. The accuracy ratio was approximately 0.8 after 3 years.

Figure 9. Line Plot of the Accuracy Ratio over Time for Individual Subjects



Reviewer's analysis based on Applicant's dataset refill.xpt. Individual subject data are connected by lines. The solid blue line is the loess trend line with 95% confidence interval shown by shading.

As shown in the table below, there is no trend in a change in the frequency of PAH symptoms (fatigue, dyspnea, edema, dizziness, syncope, chest pain) throughout study participation.

Table 27. Incidence of AEs Related to Worsening PAH**Table 12-27. Incidence of AEs Potentially Related to Worsening PAH Over Time**

Time Period (Months since Implant)	Number of Subjects	Months of Follow-up	Number of PAH-related AEs*	PAH-related AEs rate (per Subject-Month)
0 to 3	60	179.9	36	0.20
3 to 6	59	175.2	20	0.11
6 to 9	58	174.0	19	0.11
9 to 12	58	171.8	16	0.09
12 to 15	57	171.0	15	0.09
15 to 18	57	171.0	10	0.06
18 to 21	57	170.2	16	0.09
21 to 24	56	167.9	15	0.09
24 to 27	55	165.0	15	0.09
27 to 30	55	162.3	18	0.11
30 to 33	53	158.7	15	0.09
33 to 36	52	154.9	6	0.04
36 to 39	51	141.4	10	0.07
39 to 42	41	92.0	5	0.05
42 to 45	19	53.5	3	0.06
Total	60	2362.9	224	0.09

* Events that occurred on the same day in the same subject counted as one event.

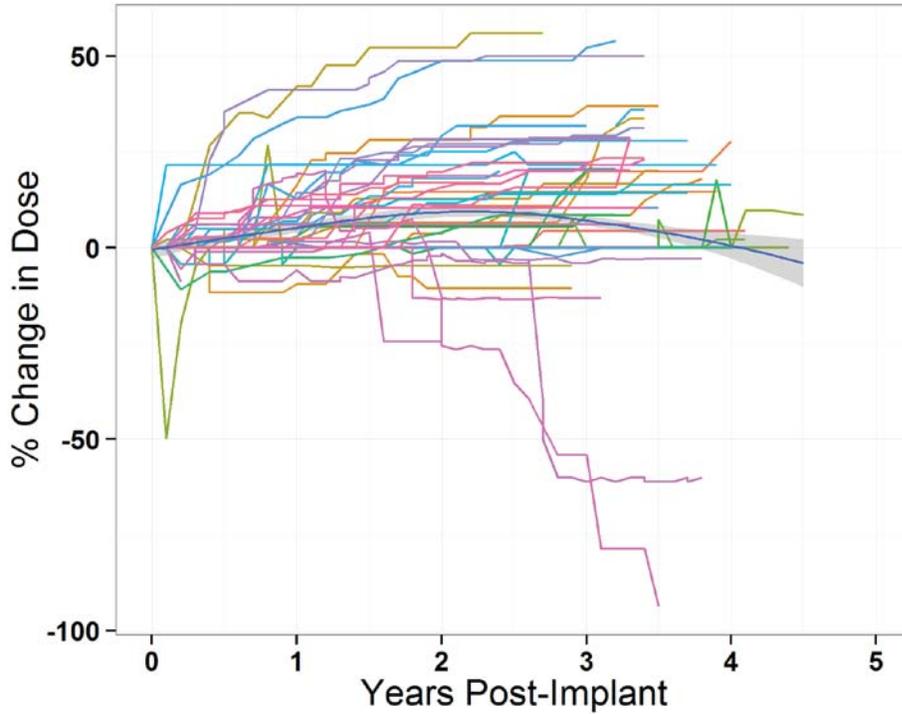
Source: pah-aes.sas

Applicant Table from Summary of Drug-Device Safety Update

There is a trend for the Remodulin dose to increase with time as shown in the following figure. At the last clinic visit as of the data cutoff date (08 Jan 2016), 22 (36.7%) of the 60 subjects were receiving the same or a lower dose than that at Baseline. There was no correlation between change in accuracy ratio and change in Remodulin dose.

Reviewer's comment: It is not clear whether the increase in dose is related to the decrease in accuracy ratio or normal clinical management of PAH subjects. According to the Orenitram USPI, the dose of Orenitram continued to increase over time.

Figure 10. Line Plot of the Change in Remodulin Dose over Time for Individual Subjects



Reviewer's analysis based on Applicant's dataset refill.xpt. Individual subject data are connected by lines. The solid blue line is the loess trend line with 95% confidence interval shown by shading.

7.5.1 Dose Dependency for Adverse Events

Not applicable.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

Not applicable.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostini. In vitro and in vivo genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostini. Treprostini did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusions at rates of up to 450 ng treprostini/kg/min [about 59 times the recommended starting human rate of infusion (1.25 ng/kg/min) and about 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a ng/m² basis]. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy Category B - In pregnant rats, continuous subcutaneous infusions of treprostini during organogenesis and late gestational development, at rates as high as 900 ng treprostini/kg/min (about 117 times the starting human rate of infusion, on a ng/m² basis and about 16 times the average rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous infusions of treprostini during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostini/kg/min (about 41 times the starting human rate of infusion, on a ng/m² basis, and 5 times the average rate used in clinical trials). In rats, continuous subcutaneous infusion of treprostini from implantation to the end of lactation, at rates of up to 450 ng treprostini/kg/min, did not affect the growth and development of offspring. Because animal reproduction studies are not always predictive of human response, Remodulin should be used during pregnancy only if clearly needed.

No treprostini treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostini sodium on labor and delivery in humans is unknown.

7.6.3 Pediatrics and Assessment of Effects on Growth

Safety and effectiveness in pediatric subjects have not been established. Clinical studies of Remodulin did not include sufficient numbers of subjects aged ≤ 16 years to determine whether they respond differently from older subjects. In general, dose selection should be cautious.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Signs and symptoms of overdose with Remodulin during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.

In controlled clinical trials, seven subjects received some level of overdose and in open-label follow-on treatment seven additional subjects received an overdose; these occurrences resulted from accidental bolus administration of Remodulin, errors in pump programmed rate of administration, and prescription of an incorrect dose. In only two cases did excess delivery of Remodulin produce an event of substantial hemodynamic concern (hypotension, near-syncope).

One pediatric subject was accidentally administered 7.5 mg of Remodulin via a central venous catheter. Symptoms included flushing, headache, nausea, vomiting, hypotension and seizure-like activity with loss of consciousness lasting several minutes. The subject subsequently recovered.

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarket Experience

In addition to adverse reactions reported from clinical trials, the following events have been identified during post-approval use of Remodulin. These events are thrombophlebitis associated with peripheral intravenous infusion, thrombocytopenia and bone pain. In addition, generalized rashes, sometimes macular or papular in nature, and cellulitis have been infrequently reported.

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/s/

MARYANN GORDON
08/03/2016

CHRISTINE E GARNETT
08/03/2016