

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**STATISTICAL REVIEW(S)**



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## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA: Supplement:** 208276  
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**Biometrics Division:** DBI/OB/OTS/CDER  
**Statistical Reviewer:** Fanhui Kong, PhD  
**Concurring Reviewers:** Hsien Ming Hung, PhD

**Medical Division:** Division of Cardiovascular and Renal Products  
**Clinical Team:** Patricia Beaston, MD  
**CDTL:** Shari Targum, MD  
**Project Manager:** Wayne Amchin,

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## 1 EXECUTIVE SUMMARY

In this NDA the Sponsor submitted a pivotal study DelIVery to assess the safety profile of the Model 10642 Implantable Intravascular Catheter for the delivery of Remodulin® (treprostinil) injection in the treatment of patients with pulmonary arterial hypertension (PAH) who met the approved Remodulin Injection indication, using the approved formulation, and approved intravenous route of administration.

The DelIVery for PAH study is a multicenter, prospective, single arm, non-randomized open label investigational clinical trial. The purpose of the trial is to evaluate the safety profile of the Model 10642 Implantable Intravascular Catheter, a component of the PAH Implantable Vasodilator Therapy (PIVoT) system, to deliver Remodulin Injection, for the treatment of PAH. The study population will include patients currently treated with the approved intravenous (IV) infusion route of delivery of Remodulin Injection for PAH.

The study was conducted at up to 10 sites in the U.S. A total of 64 subjects were enrolled and 60 were implanted of which 9 died during study participation. Given PAH is a severe and fatal disease, the serious AE rate and survival rate were consistent to those of the general PAH patient population. A total of 7 primary endpoint complications were observed during the accumulation of 71,920 patient days, resulting in a total of 0.10 catheter-related complications per 1000 patient days and the one-sided upper 97.5% confidence bound of 0.20 which is below 2.5 per 1000 patient days, the rate identified from the external Central Venous Catheter literature. This result seems to provide adequate evidence to support the safety of the Model 10642 investigational Implantable Intravascular Catheter for the delivery of Remodulin injection for the treatment of the patients with PAH.

## INTRODUCTION

Pulmonary arterial hypertension is an incurable disease with median survival approaching 7 years. Although prostacyclins are accepted as one of the most efficacious regimens, there is underutilization of the therapy. Current options allow patients continuous parenteral prostanoid therapy via an external infusion pump, either with an indwelling central venous catheter or by subcutaneous injection. This method creates fear and angst for some PAH patients. In addition, indwelling central venous catheters are associated with the risk of blood stream infections and sepsis, which can be fatal. Patients receiving subcutaneous injections often experience infusion site pain.

Medtronic, Inc. sponsored a multicenter, prospective, single arm, non-randomized open label investigational clinical trial, named “DelIVery” for PAH. The purpose of this 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 PIVoT system also includes a market approved implantable drug delivery pump with programmer (SynchroMed II), and a sutureless connector to connect the investigational catheter to the SynchroMedII pump. This fully implanted system was used to deliver the currently marketed pharmaceutical product treprostinil (Remodulin). Because Remodulin therapy is the only parenteral with a 4-hour half-life and proven long-term stability, it is the only prostacyclin candidate for the PIVoT system.

The sponsor tested the hypothesis that the investigational implantable intravascular catheter is safe when used in the PIVoT system to deliver treprostinil by demonstrating that the incidence rate of catheter-related complications is less than catheter-related complications using external systems. This drug-device combination was developed to change the current prostacyclin treatment by removing the need to prepare medication multiple times a week and wear an external pump. It minimizes the risk of bloodstream infections and generates impactful improvements in PAH patients’ lives.

### 1.1 Overview

This study focuses on the safety of delivery of Remodulin Injection 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 data generated by the study are intended to provide adequate safety information necessary to support the FDA approval of a marketing application for the Model 10642 catheter and the labeling updates for the SynchroMed II system, as well as an NDA-supplement from United Therapeutics to support the updates to Remodulin Injection labeling.

This open-label, uncontrolled study was designed to evaluate the safety of Model 10642 Implantable Intravascular Catheter when used with the Medtronic SynchroMed II Implantable Infusion System to deliver Remodulin compared with historical literature. For ancillary endpoints, data collected during the follow-up visits were analyzed by comparing with the subjects’ Baseline values (receiving Remodulin via an external infusion pump).

The original protocol was developed on October 14, 2010. The study design was conditionally approved by FDA Center for Devices and Radiological Health (CDRH) under Investigational Device Exemption (IDE) G100017 for the DelIVery for PAH clinical protocol Version 4 on January 21, 2011, limiting the study to five subjects and one U.S. institution. The protocol was amended once to allow enrollment of up to 70 subjects at 10 sites. Additionally, six IDE-supplements resulted in changes to the conduct of the study.

This NDA was first submitted on January 26, 2015 and the submission was refused to file on February 24, 2015 because the application was not sufficiently complete to permit a substantive review.

The revised NDA was submitted on December 16, 2015 which included additional analyses of the clinical study data set presented in the DelIVery for PAH, premarket application (PMA) Clinical Report for data cutoff point of July 25, 2014. On April 15, 2016, a revision was submitted with the analysis results being updated based on additional data collected by the new data cutoff date of January 08, 2016. This date will be referred to as the data cutoff date in this review. New data sets and programs were provided. This review is conducted based on the newest submission.

## **1.2 Data Sources**

The sponsor's electronic data sources were stored in the directories of [\\CDSESUB1\evsprod\NDA208276\0007\](#) and [\\CDSESUB1\evsprod\NDA208276\0010\](#) of the Center's electronic document room of the Agency. Data sources include all raw data sets in SDTM format, analysis data sets in ADAM format, individual data listings, SAS programs for deriving the data sets and analysis results, the study reports, protocol amendments, statistical analysis plan, literature referenced, etc.

## **2 STATISTICAL EVALUATION**

### **2.1 Data and Analysis Quality**

The sponsor provides high quality data sets along with the programs to produce the analysis data sets and safety results which allow the statistical reviewer to confirm the results.

Data collected include demographics, medical history, medications, adverse events, exit/death information, deviations, device malfunctions, serum treprostinil levels, fluoroscopic/radiograph images of catheter location, pump programming and fill data, New York Heart Association (NYHA) classification, physical assessment, six minute walk test, quality of life (QoL) questionnaires, and subject and caregiver involvement assessment.

According to Clinical Study Report (CSR), data were collected using an electronic data management system for clinical trials. Electronic case report form (eCRF) data were stored in a secure, password-protected database that was backed up nightly. Access to the database was restricted to trained and delegated personnel. Data were reviewed using programmed and manual data checks. Data queries were made available to sites for resolution. Study management reports were generated to monitor data quality and study progress.

Investigators were required to ensure accuracy, completeness, and timeliness of the data reported to Medtronic. Electronic case report forms were maintained and signed electronically within the electronic data capture system during the trial by authorized study site personnel. The data for this report were stored as a frozen data set and will be retained indefinitely. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

## **2.2 Evaluation of Efficacy**

The primary objective of this study was to determine the safety of the investigational catheter. An ancillary objective of the study was to determine the percent change of six-minute walk distance from baseline to six weeks post-implant and to characterize changes in quality of life (QoL). There was no primary efficacy endpoint in this study.

The percent change in six-minute walk distance from baseline to 6 weeks post-implant in meters was calculated. The mean percentage increase in six-minute walk test values in the first six weeks post implant was 0.2% (95% confidence interval: -4.9% to 5.2%).

The CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review) QoL questionnaire was given at baseline, 6-week, three-month, six-month and twelve-month follow-up visits. The CAMPHOR has three scales: symptoms, activities, and QoL, which are calculated separately. The changes in all three scale scores from baseline to six months post-implant were calculated for each subject. For categorization purposes, a decrease in the score of at least two points indicates better quality of life. An increase of at least two points indicates worse quality of life.

Mean changes of the scores from CAMPHOR between baselines and six month follow-ups with 95% confidence intervals as well as percentages of the subjects falling into each of three levels are presented (better, no change, worse) (Table 3.1). Data from all successfully implanted subjects with CAMPHOR scores at baseline and six months are included in this analysis. Changes in the three scores were minimal, with the average scores being within two of baseline, and many subjects scoring no change.

**Table 3.1 CAMPHOR Baseline to Month 6 Results  
of the Implanted Subjects**

	<b>Symptom Scale</b>	<b>Activity Scale</b>	<b>QoL Scale</b>
Mean Score Change ± SD	-0.37 ± 3.51	1.03 ± 3.10	-0.51 ± 3.07
95% Confidence Interval	(-1.32, 0.54)	(0.20, 1.85)	(-1.32, 0.30)
Change			
Better	18 (32%)	10 (18%)	18 (32%)
No Change	25 (44%)	26 (46%)	29 (51%)
Worse	14 (25%)	21 (37 %)	10 (18%)

Source: Table 11-3 in Summary of Drug-Device Safety Update: IDE G100017.

These results are expected since the treatment therapy being provided in this study was the same therapy received at baseline; only the drug delivery method of using an internal versus external drug delivery system was changed.

## **2.3 Evaluation of Safety**

### **2.3.1 Study Design and Endpoints**

It's not clear when the original Clinical Investigational Plan (CIP) was developed. The final version of the CIP (Version 5) was finished on February 2, 2011. In this CIP, the study design, primary objective, analysis endpoints and the detailed statistical analysis methods were developed. The first enrollment was on June 14, 2011.

#### **Study Design**

Study G100017 is an open-label, uncontrolled study designed to evaluate the safety of Model 10642 Implantable Intravascular Catheter when used with the Medtronic SynchroMed II Implantable Infusion System to deliver Remodulin compared with historical literature in the PAH patient population. Prior to enrollment, subjects were required to have been receiving IV Remodulin, and to have had a stable dose (no change in dose) for at least four weeks. Additionally, subjects were not to have been initiated on a new oral PAH therapy within two months prior to enrollment.

Implant of the system occurred within two weeks of the baseline visit. 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 (AEs). Clinical data were also collected at system modifications, upon notification of adverse events or device malfunctions, deviations, exits, and in cases of death or pregnancy. Subjects will continue to be followed until marketing approval is granted from the US FDA or official study closure, whichever occurs first.

### **Rationale for Study Design**

Remodulin Injection is a well-established and effective therapy for PAH. It is currently delivered subcutaneously, and intravenously (IV). Since the new delivery system delivers Remodulin Injection to the same place, effectiveness does not need to be tested. The new component in the system is the Model 10642 Implantable Intravascular Catheter. The remainder of the system, including the SynchroMed II Implantable Infusion System has been used in the market for many years. A single arm study was chosen because subjects could not be blinded and the primary safety objective is to assess the safety of the catheter, for which there is no reasonable control group.

### **Sample Size**

A total of 64 subjects were enrolled (consented) in the study at 10 US sites, and 60 subjects were successfully implanted with the system.

A total of 22,000 patient days of follow-up were estimated using a simulation program with the assumption of the rate of catheter-related complications followed a Poisson distribution with a mean rate 1.5 events per 1000 patient days to reach a power of 90% to detect the safety of the investigational catheter if the exact upper 97.5% confidence bound was below 2.5 per 1000 patient days. Implanted subjects were expected to have an average of 440 days of follow-up. A total of 50 implanted subjects were adequate to achieve 22,000 patient days. The maximum enrollment sample size was 70 subjects. Analyses were performed when subjects completed six months of follow-up and 22,000 patient days were accumulated.

The study was expected to enroll up to 70 subjects to ensure at least 50 subjects to be successfully implanted.

### **Primary Endpoints:**

The primary endpoint was related to the safety of the investigational catheter. The primary endpoint is catheter-related complications per 1000 patient days. A complication was defined as any adverse event that resulted in death, involved any termination of significant device function, or required an invasive intervention. 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 were also counted toward the primary endpoint.

According to the sponsor, the Adverse Event Advisory Committee (AEAC) adjudicated all the adverse events according to prespecified rules as catheter-related complications or just observations. If an event was classified as a complication, even its relatedness to the catheter was unknown, it was still counted as a catheter-related complication. Additionally, pneumothorax was adjudicated by the AEAC as procedure-related, and classified as a complication, was counted toward the primary endpoint. The number of patient days contributed by each subject was the latest known date of follow-up. The number of patient days for subjects who had the system explanted was the removal date minus the implant date.

### 2.3.2 Statistical Methodologies

According to sponsor, the statistical analysis plan (SAP) was developed based on the revised study protocol on January 26, 2012, before data were analyzed. According to SAP, data from all the centers that participated in this protocol were combined for analysis. Once all active subjects had completed the six month follow-up and there were at least 22,000 days of follow-up among implanted subjects, a PMA report would be prepared.

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 following hypotheses were developed.

Hypothesis:

- $H_0$ : Rate of catheter-related complications  $\geq 2.5$  per 1000 patient days
- $H_A$ : Rate of catheter-related complications  $< 2.5$  per 1000 patient days

The Model 10642 Implantable Intravascular Catheter is considered to be safe if the one-sided upper 97.5% confidence bound of the rate of catheter-related complications among all the implanted subjects is less than 2.5 per 1000 patient days. 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.

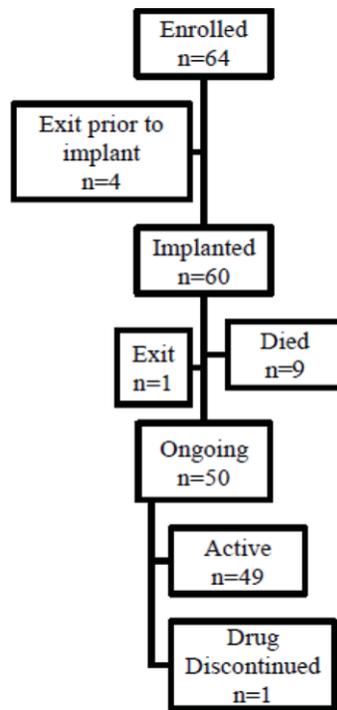
The catheter-related complication rate of 2.5 per 1000 patient days in the PAH population was a rough estimate from a series of published studies. The estimated rate of central venous catheter (CVC) systemic infections for bloodstream infections goes from 0.43 (Dicknson et al., 2009) to 1.13 (Kallen, et al., 2008) per 1000 patient days. The estimated site infection rate is from 0.26 (Oudiz, et al., 2004) to 0.87 (Akagi, et al., 2007) per 1000 patient days. Finally the combined estimated rate of complications from catheter thrombosis, mechanical dysfunction, and catheter dislocation in the general CVC population is from 0.36 (Smith, et al., 1998; Bozzetti, et al. 2002) to 0.51 (Moureau, et al., 2002) per 1000 patient days Adding the three higher estimated rates together gives a roughly estimated total rate of catheter-related complication of up to 2.5 per 1000 personal days.

### 2.3.3 Patient Disposition, Demographic and Baseline Characteristics

#### Disposition

A total of 64 subjects were enrolled (consented) in the study at 10 US sites, and 60 subjects were successfully implanted with the system. 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). Nine subjects had died and one subject had discontinued therapy due to AEs.

**Figure 3.1 Subject Disposition**



Source: Figure 10-1 in Summary of Drug-Device Safety Update: IDE G100017

#### Demographic and Other Baseline Characteristics

The demographics of the subjects in the DelIVery for PAH clinical study enrolled into this clinical study reflected those of the overall PAH patient population. Of the 60 implanted subjects, 80% were female. The mean/median age was 50.1/52.0 years with the range from 24 to 74. Additionally, 13 (22%) of the 60 implanted subjects were Asian (3%), Hispanic (13%) or African American (5%), and 47 (78%) were Caucasian.

**Table 3.2 Key Demographic/Baseline Characteristics of the Implanted Subjects**

<b>Demographic/Baseline Characteristic</b>		<b>Implanted Subjects</b>
<b>Gender</b>	Female	48 (80%)
	Male	12 (20%)
<b>Age</b>	Mean ± SD	50.1 ± 13.5
	Median	52.0
	25 <sup>th</sup> – 75 <sup>th</sup> Percentile	38 - 61
	Minimum - Maximum	24 - 74
<b>Race</b>	Asian	2 (3%)
	African American	3 (5%)
	Hispanic	8 (13%)
	Caucasian	47 (78%)

Source: Table 11-1 in Summary of Drug-Device Safety Update: IDE G100017

### **Protocol Violations/Deviations**

Overall, there were 141 study deviations among the 64 enrolled subjects. The majority of the deviations (107) were due to one or more assessments not completed or not completed per protocol.

As of the data cutoff date, there were 20 instances in 6 subjects in which the refill interval exceeded 12 weeks, the limit specified by the study procedures. In addition, three individual site personnel participated in the study prior to being approved; one subject did not complete a pregnancy test at Baseline; one subject was enrolled into this study within 30 days of exiting a drug post-market surveillance study; and one initially missed a check box on the consent form but completed it at a later date. No protocol deviations (e.g., longer than 12 week refill interval, or implant not per protocol) directly impacted the study results including the frequency of overall AEs and 6MWD results.

### **2.3.4 Safety Results and Conclusions**

According to the sponsor, all new and/or worsening AEs experienced by the subjects, including deaths, were collected throughout the study duration starting at subject enrollment and reported to the Sponsor on an AE electronic Case Report Form (eCRF). Documented pre-existing conditions were not considered AEs unless there was a change in the nature or increase in severity of the condition.

As of the data cutoff date for this report, the 60 implanted subjects averaged 3.3 years of follow up for a total of 197.0 patient-years. Fifty-one subjects completed their three year visit. The range of individual ongoing subject participation was 87 to 1,625 days. The mean Remodulin dose at Baseline was  $72.2 \pm 29.5$  ng/kg/min with a range of 22 to 160 ng/kg/min. At the most recent study visit prior to this data cutoff, the mean Remodulin dose was  $79.8 \pm 26.2$  ng/kg/min with a range of 26.9 to 142.0 ng/kg/min.

### **Brief Summary of Adverse Events**

At the time of the data cutoff for this report, 23 pre-implant AEs were reported in 17 subjects and 1,030 treatment-emergent (including 2 during implant and 1,028 post-implant) AEs had been reported in 60 subjects. Twenty AEs (in 17 subjects) were considered “unavoidable” that included AEs related to the implant procedure (such as anesthesia-related nausea/vomiting within the first 24 hours and pocket site/incisional pain that had an onset and resolution within 72 hours of the implant procedure).

The most common post-implant AEs (including unavoidable AEs) were implant site pain, upper respiratory tract infection, worsening PAH, dyspnea, injection site reaction, headache, nausea, hypotension, fatigue, injection site pain, and dizziness. Of the 1,028 post-implant AEs, 294 in 59 subjects were considered related to Remodulin, one or more system components and/or a study procedure.

A total of 146 post-implant SAEs occurred in 45 of the 60 implanted subjects. Twenty-three post implant SAEs in 16 subjects were considered related to Remodulin or one or more system components or study procedures. Nine subjects died during this analysis period resulting in a survival probability of 95% at one year after enrollment into the study and 90% two years after enrollment. None of these deaths were adjudicated to be related to Remodulin, a study procedure, or any component of the system. One subject exited the study after the system was explanted due to AEs, and one subject had Remodulin replaced with saline in the pump in preparation for lung transplant.

### **Primary Analysis of Primary Safety Endpoint**

As of the data cutoff date, six catheter-related complications (all requiring invasive system modifications) and one procedure-related pneumothorax complication had occurred in this study. One subject 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.

According to the pre-defined performance goal, the safety objective on the primary endpoint would be met 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. A total of 7 primary endpoint complications were observed during 71,920 patient days, resulting in a total of 0.10 catheter-related complications per 1,000 patient days (one sided upper 97.5% confidence bound of 0.20).

These 7 complications included 3 catheter dislocations, 2 punctured catheters, one pneumothorax and one venous stenosis.

### **Statistical Comments:**

1. *The statistical method is considered to be acceptable given the study design. However, considering that this was an open label study and there was no control arm, the reliability of the statistical result could be a concern.*
2. *Due to the change of the data cutoff date, the efficacy results as well as safety results need to be updated although this does not change the safety conclusion of the study.*

### **Adverse Events other than the Primary Endpoints**

The following adverse events results are extracted from the Summary of Drug-Device Safety report submitted by the sponsor.

Of the 1,028 post-implant AEs that occurred during the study, 294 events were considered related to Remodulin. As of the data cutoff date, 1,798 pump refills had been conducted with subjects having an average of 45 days between refills. Eighty-five AEs related to the refill process occurred in 34 subjects.

A total of 164 post-implant AEs (including unavoidable AEs) were considered to be related to the implant procedure or a system modification. A system modification was required when the implanted catheter and / or pump required invasive modification. Of the 164 AEs related to implant or system modification, 22 events in 13 subjects were also considered to be related to Remodulin.

Fourteen AEs in 11 subjects were related to the SynchroMed II pump. The events of implant site extravasation (2 events), device dislocation (flipped pump) and muscle spasms were also related to the implant procedure. Five AEs in three subjects (including dyspnea, renal failure, deep vein thrombosis, and two cases of thrombophlebitis superficial) were considered to be related to the implant procedure and potentially associated with a thromboembolic event.

A total of 180 infection AEs occurred in 54 (90%) subjects during the study. These include all AEs under the MedDRA SOC of Infections and Infestations, plus all reports of general fevers, post operation fevers, phlebitis, diarrhea, and other events treated with antibiotics or associated with positive cultures noted in the diagnostic testing. Of the 180 infections, 176 in 52 (87%) subjects occurred post implant and 4 occurred prior to the implant. Eight infection-related AEs in 5 subjects were considered related to the original implant procedure or a system modification. The remaining 172 were considered unrelated to any other study procedure, a system component, or Remodulin.

The implant process has the potential to increase the risk of thrombotic / embolic events. A total of 25 AEs in 18 (30.0%) subjects fit into this category. Of these, five events in three (5.0%)

subjects were adjudicated as being related to the implant procedure. The remaining 20 events in this category were adjudicated to be unrelated to any other study procedure, a system component, or Remodulin.

To examine the potential impact of the implant process on arrhythmias, an analysis of arrhythmias present both before and after implant was conducted. Twenty-two subjects (36.7%) had a history of at least one reported arrhythmia at baseline. Twelve subjects (20%) had a history of atrial arrhythmia, two (3.3%) had a history of ventricular arrhythmia, and four (6.7%) had a history of AV junctional arrhythmia and blocks. Additionally, one subject (1.7%) had a history of both atrial and ventricular arrhythmia, two (3.3%) had a history of atrial arrhythmia and AV junctional arrhythmia and blocks, and one (1.7%) had a history of all three classes of arrhythmias at Baseline.

There were 7 system modifications in 3 of 60 implanted subjects. Five of the system modifications were due to catheter-related complications in two subjects. In this study there were no catheter-related site infections, catheter disconnects, catheter occlusions, catheter breakage, catheter thrombosis, or catheter-related bloodstream infections. There was one bloodstream infection related to a system modification procedure, but it was not related to the catheter and therefore was not counted as a primary endpoint event.

On March 13, 2012, the Sponsor 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 26 of 65 (40%) catheter implants (including catheter replacements). The Catheter Technical Manual and the System Implant Outline were updated to train implanting clinicians on new anchoring instructions. After the procedure was updated, 39 additional implants or catheter changeouts were completed with no catheter dislodgments.

## **Death and Other Serious Adverse Events**

One hundred forty-seven treatment emergent AEs in 45 subjects were serious (including one SAE that occurred during implant). Nine subjects died during study participation to the data cutoff date resulting in a survival probability of 95%, 92%, and 87% at one, two and three years after enrollment into the study, respectively. All deaths were adjudicated as not due to Remodulin or any system component or procedure. PAH is a severe and fatal disease with an estimated survival probability of 85%, 68%, 57% and 49% at 1, 3, 5 and 7 years from diagnosis, respectively (Benza, 2012).

A total of 146 SAEs occurred post implant in 45 of the 60 implanted subjects (67%). Additionally, one SAE (pneumothorax) occurred during implant, and 5 SAEs occurred pre-implant (including 4 infections and one atrial flutter). Two of the subjects with serious pre-implant infections were not implanted. Thirty-three SAEs that occurred during or post implant were related to Remodulin and/or one or more system component/study procedure. No SAEs were considered related to the programmer, catheter patency test, the catheter access port kit, or the SynchroMed II pump.

### **3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

Women represented 80% of the subjects enrolled in the study. The mean age of the subjects enrolled was 50 years. Additionally, 13 (22%) of the 60 implanted subjects in the DelIVery for PAH clinical study were Asian (3%), Hispanic (13%) or African American (5%).

Overall, AEs occurred in similar proportions across the demographic subgroups of gender, age and race as seen in Table 12-10 of Summary of Drug-Device Safety Update: IDE G100017 submitted by the sponsor. It does not seem to have any age- or gender- linked patterns in the AEs encountered. Further, the implant of the system does not seem to increase the risk of infections, thromboembolic events, or arrhythmias.

### **4 SUMMARY AND CONCLUSIONS**

#### **5.1 Statistical Issues**

The study design and statistical analysis methods seem to be appropriate for the assessment of the safety of the Model 10642 investigational Implantable Intravascular Catheter in the rate of catheter-related complications.

#### **4.2 Collective Evidence**

This is a multicenter, prospective, single arm, non-randomized open label investigational clinical trial, evaluating the safety of the Model 10642 investigational Implantable Intravascular Catheter, a component of the PIVoT System for the deliverance of Remodulin in the treatment of patients with PAH. The system also includes the SynchroMed II Implantable Infusion System (Model 8637) and the N'Vision Clinician Programmer (Model 8840) with SynchroMed II application software (Model 8870). As of the data cutoff date, the 60 implanted subjects had averaged 3.3 years of follow-up for a total of 197.0 patient-years, with the maximum follow-up of approximately 4.5 years.

The primary safety endpoint of the study was the rate of catheter-related complications per 1,000 patient days. A total of 7 primary endpoint complications were observed during 71,920 patient days that gave a one sided upper 97.5% confidence bound of 0.20, which was below 2.5 per 1000 patient days, the rate derived from reviewing the external Central Venous Catheter literature which was prespecified as being safe. This result supports the safety of the Model 10642 investigational Implantable Intravascular Catheter. The 7 catheter-related complications included 3 catheter dislocations, 2 punctured catheters, one pneumothorax and one venous stenosis. The rate of catheter-related complications in this study is significantly less than that in patients with external central venous catheters. There were no catheter-related site infections, catheter disconnects, catheter occlusions, catheter breakage, catheter thrombosis, or catheter-related bloodstream infections.

There were 147 serious treatment emergent AEs in 45 subjects (including one SAE that occurred during implant). Nine subjects died during study participation. Given PAH is a severe and fatal disease, the serious AE rate and survival rate were compatible with those of the general PAH patient population.

### 4.3 Conclusions and Recommendations

This is a multicenter, prospective, single arm, non-randomized open label investigational clinical trial, evaluating the safety of the Model 10642 investigational Implantable Intravascular Catheter, a component of the PIVoT System for the deliverance of Remodulin in the treatment of patients with PAH. As of the data cutoff date, the 60 implanted subjects had averaged 3.3 years of follow-up with the maximum follow-up of approximately 4.5 years. The primary safety endpoint of the study was the rate of catheter-related complications per 1,000 patient days. A total of 7 primary endpoint complications were observed during 71,920 patient days that gave a one sided upper 97.5% confidence bound of 0.20, which is below 2.5 per 1000 patient days, the rate identified from the external Central Venous Catheter literature. This result seems to provide adequate evidence to support the safety of the Model 10642 investigational Implantable Intravascular Catheter for the delivery of Remodulin Injection for the treatment of patients with PAH. Given PAH is a severe and fatal disease, the serious AE rate and survival rate appeared consistent to those of the general PAH patient population.

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FANHUI KONG  
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HSIEN MING J HUNG  
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