CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA: Supplement:	208276
Drug Name:	Remodulin Implantable System (RIS)
Indication(s):	Pulmonary Arterial Hypertension
Applicant:	United Therapeutics Corporation
Date(s):	December 16, 2015
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Table of Contents

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).

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