Clinical Study Report

1. TITLE PAGE

Report Title:	**F**ontan **U**denafil **E**xercise **L**ongitudinal Assessment Trial (FUEL)
Protocol Number:	PHN-Udenafil-02
NCT Number:	NCT02741115
Study Phase:	3
Investigational Drug Product(s):	Udenafil tablets 87.5 mg BID and matching placebo
Indication Studied:	Treatment of single ventricle heart disease in adolescents with Fontan physiology.
Study Period:	First subject consent: 25 July 2016 Last Week 26 visit: 27 December 2018
Clinical Investigator(s):	Multicenter
Sponsor:	Mezzion Pharma Co. Ltd in partnership with Pediatric Heart Network (PHN)
Issue Date:	**27 February 2021**

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonised Tripartite Guideline.

2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Mezzion Pharma Co. Ltd in partnership with Pediatric Heart Network (PHN)</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Udenafil tablet 87.5 mg</td></tr>
<tr><td>Name of Active Ingredient:
Udenafil</td></tr>
<tr><td colspan="3">Title of Study:
A Phase III Safety Extension Study of Udenafil in Adolescents with Single Ventricle Physiology After Fontan Palliation (FUEL Extension)</td></tr>
<tr><td colspan="3">Principal Investigator:
Multicenter
Investigators:
A list of investigators and their curricula vitae are provided in Appendix 16.1.4.</td></tr>
<tr><td colspan="3">Study center(s):
27 sites (25 United States, 2 Canada)</td></tr>
<tr><td colspan="3">Publications (reference):
None</td></tr>
<tr><td colspan="2">Studied period (years):
Date of first informed consent: 06 February 2017
Date of data cutoff: 31 August 2020</td><td>Phase of development:
3</td></tr>
<tr><td colspan="3">Objectives:
• Determine the safety of udenafil (87.5 mg twice daily [BID]) in an adolescent population with single ventricle congenital heart disease palliated with the Fontan procedure.
• Evaluate the pharmacodynamic profile of udenafil.</td></tr>
</table>

Methodology:

This was a Phase 3, open-label extension, 12-month, multicenter study, with an option for up to an additional 36 months, to supplement the Phase 3 **F**ontan **U**denafil **E**xercise **L**ongitudinal Assessment Trial (FUEL study) by providing a more robust safety and side-effect profile of the use of udenafil in adolescents with Fontan physiology. An attempt was made to recruit all participants who completed the FUEL study (approximately 400 adolescents). If recruitment from the FUEL study was less than 300 subjects, additional adolescents with Fontan physiology (De Novo subjects) were identified through the review of clinical data records at each participating site until the minimum of 300 total subjects were enrolled.

Those who were interested were enrolled and consented at the first study visit by the study coordinator from each participating site. Screening and identification of potential subjects continued until enrollment was complete.

Subjects who agreed to participate had baseline testing performed to determine eligibility with inclusion/exclusion criteria. For subjects who participated in the FUEL study and continued on to this extension study, safety laboratory results from FUEL were accepted as meeting the inclusion criteria for FUEL Extension. For De Novo subjects, the baseline visit consisted of 2 parts, baseline testing and study drug initiation. These parts may have been combined into a single day or split into 2 days so long as the duration between the visits was no more than 7 days. Safety laboratory testing and pregnancy testing for female participants were performed. After safety laboratory testing, subjects performed an exercise test to maximal effort to be eligible for study drug initiation.

All enrolled subjects were provided with udenafil, at a dose of 87.5 mg BID, for the duration of the study. The first dose of study drug was administered at the clinic (Visit 1). Approximately 2 hours (±30 minutes) post dosing, resting heart rate and blood pressure were measured, and the subject performed a self-limited 6-minute walk. A repeat heart rate and blood pressure were measured immediately following and approximately 2 hours (±30 minutes) following the 6-minute walk. Subjects who had a drop in systolic blood pressure >20 mmHg from the pre- to post-6-minute walk measurement, or had a drop in systolic blood pressure below the 5th percentile for age, were excluded from receiving any further study drug. Continuing subjects were dispensed their initial supply of study medication and instructed to take 1 tablet orally BID.

Methodology (continued):

All subjects returned to the clinic at Week 52. In addition to clinic visits, study coordinators contacted each subject by telephone the day after the baseline visit to discuss any adverse events (AEs). Subjects were also contacted by telephone at Weeks 1, 2, 3, 4, 8, 13, 17, 21, 30, 34, 39, 43, and 47 to ensure the study drug was well tolerated, to monitor study drug adherence, record AEs and concomitant medications, and offer pregnancy counseling, if needed. Subjects were encouraged to notify the study coordinator between scheduled contact dates with any new onset symptoms or complications.

For subjects continuing in FUEL Extension beyond Week 52, telephone contact occurred monthly and 30 and 90 days following study drug discontinuation to ensure the study drug was well tolerated and record AEs.

In-clinic study visits included assessments of safety (AEs, concomitant medication use, vital signs, and clinical safety laboratory evaluations), efficacy (exercise testing, echocardiogram, EndoPAT®, brain natriuretic peptide, and quality of life measurements), and pharmacokinetics.

The duration of study drug dosing was 12 months, with an option to extend for up to an additional 36 months. When an individual subject completed the study, the subject's primary cardiologist was notified, and the study drug was stopped.

De Novo subjects who were not participants in the FUEL trial were given the opportunity to participate in the heart rhythm-monitoring subset of FUEL Extension. Optional heart rhythm monitoring was to include a 3- to 7-day baseline monitor and a 3-day steady-state monitor.

Number of patients (planned and analyzed):

Planned: 300 to 400 adolescents.

Analyzed: 301 adolescents for safety (at interim analysis).

Diagnosis and main criteria for inclusion:

1. Males and females with Fontan physiology who participated in the FUEL trial or, if they did not participate in FUEL, were 12 to less than 19 years of age at enrollment.
2. Current anti-platelet or anticoagulant therapy.

Test product, dose and mode of administration, batch number:

Udenafil tablets 87.5 mg orally BID

Dr. Reddy's Laboratories Ltd.: Batches UDBT15-11 and UDBT15-12
Halo Pharmaceutical Canada, Inc.: Batch MP0220

Duration of treatment:

52 weeks, with an option to extend for up to an additional 36 months

Reference therapy, dose and mode of administration, batch number:

None

Criteria for evaluation at interim analysis:

Efficacy endpoints:

- Change in maximal VO_2 from baseline to Week 52
- Change in VO_2 at ventilatory anaerobic threshold (VAT) from baseline to Week 52
- Change in ventilatory equivalents of carbon dioxide (VE/VCO_2) at peak exercise from baseline to Week 52
- Change in VE/VCO_2 at VAT from baseline to Week 52
- Change in minute ventilation at peak exercise
- Change in work rate at peak exercise from baseline to Week 52
- Change in work rate at VAT from baseline to Week 52
- Change in myocardial performance index (MPI) from baseline to Week 52

Safety:

Adverse events, vital signs (blood pressure and heart rate), and concomitant medication use.

Statistical methods at interim analysis:

The Safety population included all subjects who took at least 1 dose of study drug. The Efficacy population included all enrolled subjects who had baseline and Week 52 exercise capacity data for which site-based data quality assurance process was complete at data cut-off.

Three treatment groups were defined:

- Udenafil-Udenafil, which included subjects who received udenafil in the FUEL and FUEL Extension studies
- Placebo-Udenafil, which included subjects who received placebo in the FUEL study and udenafil in FUEL Extension
- De Novo: Subjects who did not participate in the FUEL study and received udenafil in FUEL Extension

For efficacy and safety summaries, the Placebo-Udenafil and De Novo groups were combined (denoted as Placebo/De Novo-Udenafil).

All summaries were descriptive. Descriptive statistics for categorical endpoints included the number and percent of subjects in each treatment group and category. Quantitative endpoints were summarized for each treatment group with the mean, median, standard deviation, minimum value, and maximum value. Missing data were not imputed.

Baseline was defined as the last measurement before receipt of udenafil in FUEL Extension. For the Udenafil-Udenafil group, change to Week 52 of FUEL Extension measures change in exercise capacity between 26 weeks and 78 weeks of udenafil treatment. This change represents persistence of initial effectiveness beyond 26 weeks. For the Placebo-Udenafil and De Novo groups, change to Week 52 of FUEL Extension measures change in exercise capacity from pre-udenafil to following 52 weeks of udenafil treatment.

Statistical methods (continued):

For each efficacy endpoint, descriptive statistics were summarized for baseline, Week 52, and Week 52 change from baseline. A 2-sided, 95% confidence interval was calculated for change from baseline for each group.

Safety analyses were descriptive with no formal hypothesis testing. All AEs were classified by the Medical Dictionary for Regulatory Activities with respect to system organ class and preferred term. Subject incidence of all treatment-emergent adverse events (TEAEs), and TEAEs that are treatment-related, serious, serious treatment-related, and any TEAE leading to study discontinuation were tabulated. Number (%) of subjects who were hospitalized, had a cardiac transplant, or died were tabulated.

Incidence of potentially clinically significant changes from pre dose values in blood pressure and heart rate were tabulated at i) post first study dose but before the self-limited 6-minute walk, ii) after the 6-minute walk, and iii) at any time after dosing.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

For the Udenafil-Udenafil group, change to Week 52 of FUEL Extension measures change in exercise capacity between 26 weeks and 78 weeks of udenafil treatment. This change represents persistence of initial effectiveness beyond 26 weeks. For the Placebo/De Novo-Udenafil group, change to Week 52 of FUEL Extension measures change in exercise capacity from pre-udenafil to after 52 weeks of udenafil treatment.

In the Placebo/De Novo-Udenafil group, mean exercise capacity and myocardial performance improved between pre-udenafil and after 52 weeks of udenafil treatment:

- Mean increase at peak exercise effort in VO_2 (58.00 mL/min), work rate (5.78 watts), and minute ventilation (2.41 L/min). When VO_2 was standardized by each subject's body weight, a mean decrease was observed (-0.93 mL/kg/min; 95% CI: -1.7 to -0.2 mL/kg/min).
- Mean increase in VO_2 at VAT of 12.90 mL/min (95% confidence interval [CI]: -23.1 to 48.9 mL/min). When standardized by each subject's body weight, a mean decrease was observed (-0.93 mL/kg/min; 95% CI: -1.5 to -0.4 mL/kg/min).
- Mean decrease in VE/VCO_2 at VAT of -0.77 (95% CI: -1.4 to -0.2).
- Mean increase in work rate at VAT of 0.58 watts (95% CI: -2.6 to 3.7 watts).
- Mean decrease in MPI of -0.04 (95% CI: -0.1 to 0.0).

In the Udenafil-Udenafil group, mean exercise capacity was improved while myocardial performance did not deteriorate between 26 weeks and 78 weeks of udenafil treatment:

- Mean increase at peak exercise effort in VO_2 (38.00 mL/min), work rate (2.99 watts), and minute ventilation (2.56 L/min). When VO_2 was standardized by each subject's body weight, a mean decrease was observed (-1.45 mL/kg/min; 95% CI: -2.3 to -0.6 mL/kg/min).
- Mean increase in VO_2 at VAT of 6.57 mL/min (95% CI: -47.9 to 61.0 mL/min). When standardized by each subject's body weight, a mean decrease was observed (-1.25 mL/kg/min; 95% CI: -2.1 to -0.4 mL/kg/min).
- Mean decrease in VE/VCO_2 at VAT of -0.66 (95% CI: -1.6 to 0.3).
- Mean increase in work rate at VAT of 0.26 watts (95% CI: -5.1 to 5.6 watts).
- Negligible mean decrease in MPI of -0.0 (95% CI: 0.0 to 0.0).

SAFETY RESULTS:

No clinically important differences were observed in the safety profile between subjects who had previously received treatment with udenafil and those who were naïve to udenafil treatment prior to participating in this study.

Similar percentages of subjects in the Udenafil-Udenafil and Placebo/De Novo-Udenafil groups reported TEAEs (77.3% and 80.3%, respectively), drug-related TEAEs (64.1% and 67.6%, respectively), TEAEs of Grade ≥3 (3.9% and 7.5%, respectively), serious TEAEs (10.9% and 13.9%, respectively), drug-related serious TEAEs (3.9% and 5.8%, respectively), and TEAEs resulting in temporary or permanent discontinuation of study drug (15.6% and 12.7%, respectively).

The most common TEAEs reported included headache (35.2%), flushing (17.2%), dizziness (11.7%), upper respiratory tract infection (10.2%), and nausea (10.2%) in the Udenafil-Udenafil group and headache (40.5%), flushing (15.6%), nasopharyngitis (12.7%), and dizziness (12.7%) in the Placebo/De Novo-Udenafil group. Most TEAEs were mild or moderate in intensity; similar percentages of subjects in the Udenafil-Udenafil (5 subjects; 3.9%) and Placebo/De Novo-Udenafil (13 subjects; 7.5%) groups experienced a severe TEAE.

There was no clinically important difference in the TEAE profile among males and females; the limited number of non-Caucasian subjects and Hispanic or Latino/Latina subjects precluded meaningful comparisons between race and ethnicities within treatment groups.

No subject died during the study. At least 1 serious TEAE was reported by 14 (10.9%) subjects in the Udenafil-Udenafil group and 24 (13.9%) subjects in the Placebo/De Novo-Udenafil group. Among the serious TEAEs reported, cardiac failure was reported by 4 subjects in the Placebo/De Novo Udenafil group, transient ischaemic attack was reported by 2 subjects in the Placebo/De Novo Udenafil group and 1 subject in the Udenafil-Udenafil group, abdominal pain and appendicitis were reported by 2 subjects each in the Udenafil-Udenafil group, protein-losing gastroenteropathy, gastroenteritis, and syncope were reported by 2 subjects each in the Placebo/De Novo Udenafil group, and anaemia, supraventricular tachycardia, ventricular tachycardia, and vomiting were reported by 1 subject each in the Udenafil-Udenafil and Placebo/De Novo Udenafil groups. All other serious TEAEs were reported by no more than a single subject in either treatment group. Hospitalization was reported for 14 (10.9%) subjects in the Udenafil-Udenafil group and for 24 (13.9%) subjects in the Placebo/De Novo Udenafil group. No transplants were reported.

At least 1 TEAE leading to temporary or permanent discontinuation of study drug was reported by 20 (15.6%) subjects in the Udenafil-Udenafil group and 22 (12.7%) subjects in the Placebo/De Novo-Udenafil group. The most common types of TEAEs that led to temporary or permanent discontinuation of study drug were associated with nervous system disorders including headache (2 Udenafil-Udenafil, 4 Placebo/De Novo-Udenafil), migraine (2 Udenafil-Udenafil, 2 Placebo/De Novo-Udenafil), and dizziness (1 Udenafil-Udenafil, 2 Placebo/De Novo-Udenafil).

Dizziness was the most commonly reported TEAE of special interest (11.7% Udenafil-Udenafil and 12.7% Placebo/De Novo-Udenafil). None of the events of dizziness was serious, all were considered mild or moderate in intensity and most required no change in study drug. The other TEAEs of interest including syncope, presyncope, and hypotension occurred in <4% of subjects in either treatment group.

No clinically important findings were observed in the evaluations of vital signs.

CONCLUSION:

Improvement in exercise capacity was observed in those who were previously naïve to udenafil therapy, and there was persistence of effect on exercise capacity for those who were previously treated with udenafil. Udenafil administered orally at 87.5 mg BID for 52 weeks was safe and well tolerated in this study.

Date of the report: 25 February 2021

3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

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4 List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	adverse event
ANCOVA	analysis of covariance
BID	twice daily
BNP	brain natriuretic peptide
CPET	cardiopulmonary exercise stress test
CVP	central venous pressure
CYP	cytochrome P450
DCC	data coordinating center
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
FUEL	Fontan Udenafil Exercise Longitudinal (Assessment Trial)
ICF	informed consent form
IRB	Institutional Review Board
ITT	intent-to-treat
InRHI	log transformed reactive hyperemia index (ie, the PAT index)
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MPI	myocardial performance index
NHLBI	National Heart, Lung, and Blood Institute
PAT	pulse amplitude tonometry
PCQLI	Pediatric Cardiac Quality of Life Inventory
PDE-5	phosphodiesterase type 5 (inhibitor)
PedsQL	Pediatric Quality of Life Inventory
PHN	Pediatric Heart Network
PK	pharmacokinetic
PVR	pulmonary vascular resistance
Qp	transpulmonary blood flow
REB	Research Ethics Board
RER	respiratory exchange ratio
RHI	reactive hyperemia index (ie, the PAT index)
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event
VAT	ventilatory anaerobic threshold
VE/VCO_2	ventilatory equivalents of carbon dioxide
VO_2	minute oxygen consumption

Note: Abbreviations used only in a table or figure are defined with the table or figure.

5 Ethics

5.1 Independent Ethics Committee or Institutional Review Board

An Institutional Review Board (IRB) or Research Ethics Board (REB) reviewed and approved the protocol and the informed consent form (ICF)/assent forms for each of the investigational sites prior to the first dose administration. The first informed consent was signed on 27 July 2016, and the last Week 26 visit was conducted on 27 December 2018.

A copy of the final protocol (Protocol PHN-Udenafil-02, dated 31 August 2017) is provided in Appendix 16.1.1 and a sample electronic case report form (eCRF) is provided in Appendix 16.1.2. The name, address, and chairperson of each IRB/REB, and dates of IRB/REB approval for the protocol and ICF/assent forms are provided in Appendix 16.1.3.

5.2 Ethical Conduct of the Study

This study was conducted in accordance with the International Council for Harmonisation, Harmonised Tripartite Guideline for Good Clinical Practice, 1997; the United States Title 21 Code of Federal Regulations Parts 50, 56, and 312; and the ethical principles that have their origin in the Declaration of Helsinki.

5.3 Subject Information and Consent

Subjects were approached for participation, either in person or by telephone, by study coordinators or Investigators, who obtained assent and/or consent following standard Pediatric Heart Network (PHN) procedures. The specific consent/assent procedures were in compliance with the requirements of each site's IRB/REB. Prior to the performance of any study-related procedures, the subject or subject's parent/legal guardian signed and dated an ICF. Subjects younger than 18 years of age (or as required by state law) signed an assent form. The consent process involved separate consent forms and signatures indicating consent for participation in the udenafil study and consent to submit a blood sample to the genetic biorepository. Sample ICF and assent forms are provided in Appendix 16.1.3.

Each subject was assigned a subject identification number. All interview and clinical research data were stripped of identifiers and labeled with the subject identification number. The enrollment log with participant identifiers was maintained at each site in a secured, locked location available only to the study staff. Samples for DNA were stripped of the subject identification number at the laboratory and assigned distinct specimen numbers without other identifying information.

6 Investigators and Study Administrative Structure

The study was conducted at 30 study centers in North America and the Republic of Korea. Only Investigators qualified by training and experience were selected as appropriate experts to investigate the study drug. At each study site, the Principal Investigator at that site was responsible for study activities. A list of Investigators and their curricula vitae are provided in Appendix 16.1.4. Roles and qualifications of other staff whose participation materially affected the conduct of the study, including the author(s) of the clinical study report and the responsible biostatistician(s), are also listed in Appendix 16.1.4. The Sponsors' approval of this clinical study report is located in Appendix 16.1.5.

The study was monitored by a Data and Safety Monitoring Board (DSMB), which advised the Sponsor regarding the continuing safety of study subjects and potential subjects, as well as continuing validity and scientific merit of the trial. The details regarding frequency of meetings, members and the safety review criteria were outlined in a separate DSMB Charter (Appendix 16.1.3). The logistics of the DSMB were managed by the National Heart, Lung, and Blood Institute (NHLBI), which appointed the DSMB, HealthCore (previously the New England Research Institutes), and a blinded statistician from the biostatistics department of HealthCore performed the analyses. No major recommendations regarding study conduct were made based on the reviews of the safety data.

A tabular display of study responsibilities is presented in Table 1.

Table 1: Table of Study Responsibilities

Sponsor:	Mezzion Pharma Co. Ltd in Partnership with the Pediatric Heart Network (PHN) Mezzion Pharma Co. Ltd 7F, Seokcheon Building 570, Samseong-ro Gangnam-gu Seoul, South Korea 06163
Sponsor Representatives:	James Yeager, RPh, PhD
Study Medical Monitor:	Brian Feingold, MD, MS, FAHA University of Pittsburgh School of Medicine
Coordinating Principal Investigators:	David Goldberg, MD Stephen Paridon, MD Children's Hospital of Philadelphia
Contract Research Organization (monitoring, data management, and statistical, and pharmacokinetic analysis):	HealthCore (previously New England Research Institutes) 480 Pleasant Street Watertown, MA 02472
Contract Research Organization (statistical analysis and narrative writing as of 09 August 2019)	DZS Clinical Services 1661 U.S. 22 West Bound Brook, NJ 08805
Electronic Data Capture:	HealthCore (see above)
Interactive Web Response System:	HealthCore (see above)
Data and Safety Monitoring Board Managing Organization:	Data and Safety Monitoring Board for the Pediatric Heart Network, administered by the National Heart, Lung, and Blood Institute
Clinical Drug Supply and Distribution:	Fisher Clinical Services, Inc 699 N. Wheeling Road Mount Prospect, IL 60056
Central Laboratories:	MMGL Molecular Genetics Laboratory, University of Michigan, Room 3725, Med Sci II, 1150 West Medical Center Drive, SPC 5629 Ann Arbor, MI 48109-5629
Pharmacokinetic Laboratory:	Nuvisan Pharma Services, Nuvisan GmbH Wegenerstraße 13 89231 Neu-Ulm Germany
Echocardiogram Core Laboratory:	Boston Children's Hospital Corporation 300 Longwood Avenue Boston, MA 02115
Vascular Core Laboratory:	Cincinnati Children's Hospital Medical Center 3333 Burnet Avenue., MLC 7002 Cincinnati, OH 45229
Biomarker Analysis Laboratory:	Cincinnati Children's Hospital Medical Center 3333 Burnet Avenue, MLC 7002 Cincinnati, OH 45229 MMGL Molecular Genetics Laboratory University of Michigan, Room 3725, Med Sci II, 1150 West Medical Center Drive, SPC 5629 Ann Arbor, MI 48109-5629
Medical Writing:	WebbWrites, LLC 1904 Front Street, Building 600 Durham, NC 27705

7 Introduction

The overall aim of the **F**ontan **U**denafil **E**xercise **L**ongitudinal Assessment (FUEL) trial was to evaluate the efficacy and safety of udenafil as a therapeutic option for those born with single ventricle heart disease who have undergone Fontan palliation. This study was conducted in coordination with the PHN, a consortium of congenital heart centers under the leadership of the NHLBI. At present, medical therapy for these patients is extrapolated from experience with adult-onset systolic heart failure, a condition distinct from the heart failure state associated with the Fontan circulation. The development of a medication specific to the physiology following Fontan palliation would represent a major therapeutic advancement in the field, as there are currently no approved pharmacotherapies for this unique cohort of patients.

The Fontan operation is a palliative procedure for children born with a rare group of congenital heart defects characterized by a single functional ventricle (Fontan 1971; Kreutzer 1973). This operation, which creates a total cavopulmonary connection, separates the systemic and pulmonary circulations, and reduces the hypoxemia and ventricular volume overload characteristic of single ventricle heart disease. After the Fontan, the single cardiac ventricle is surgically assigned to pump blood only to the systemic circulation. Flow through the pulmonary circulation, now without the assistance of a pumping chamber, is dependent on the gradient between central venous pressure (CVP) and atrial pressure, and on the maintenance of low pulmonary vascular resistance (PVR). The introduction of the Fontan operation has significantly improved the morbidity and mortality burden of single ventricle heart disease through childhood, but has also created a unique population with a substantial need for ongoing cardiac care and intervention, and a limited life expectancy. Although the Fontan operation is initially well tolerated, the unique characteristics of the total cavopulmonary connection lead to progressive cardiovascular dysfunction over time.

Exercise performance is a key metric of cardiovascular health for a variety of congenital and acquired forms of heart disease. For those who have undergone Fontan palliation, this relationship may hold particular importance (Diller 2005; Diller 2010; Fernandes 2011; Cunningham 2017). The decline in exercise capacity that typically occurs in the second and third decade after the Fontan is associated with an increase in the need for heart failure medications, an increase in the need for hospitalization, and an increase in the prevalence of both heart transplantation and mortality. The limitations in exercise capacity in the Fontan circulation are related to the absence of a sub-pulmonary ventricle. Without a pumping chamber to help deliver blood through the lungs and back to the heart, the ability to increase cardiac output is dependent on low PVR and an elevation in CVP. In a 2-ventricle circulation,

an increase in right-heart pressure to nearly 50 mmHg is key to reaching the increase in cardiac output of 4-fold or greater seen at peak exercise (Stickland 2006; Argiento 2010). In a single ventricle circulation, however, CVP cannot reach a pressure near that which can be achieved by a typical right ventricle. In this setting, the ability to augment cardiac output is limited and the role of PVR during exercise is magnified (Goldberg 2013; Navaratnam 2016; Egbe 2017). By minimizing PVR, one can decongest the venous system at baseline and allow for an improvement in the ability to increase flow through the pulmonary vasculature during exercise (Gewillig 2010; Goldstein 2010; La Gerche 2010).

Udenafil is a selective, long-acting phosphodiesterase type 5 (PDE-5) inhibitor that has unique characteristics within the class and has demonstrated effectiveness as a pulmonary vasodilator in the treatment of patients with pulmonary hypertension (Chang SA 2019; Chang H-J 2019). Given the need for a medication specific to those with a total cavopulmonary connection, Mezzion Pharma Co. Ltd, in partnership with the PHN, has developed udenafil as a potential therapeutic option for those who have undergone the Fontan procedure. At present, udenafil is the only pharmacotherapy to have undergone pharmacokinetic (PK) analysis through a Phase 1/2 dose-finding study in this population. This study demonstrated that a dose of 87.5 mg twice daily (BID) provided the highest maximal plasma concentration with an acceptable drug tolerability and a clinical improvement in ventricular performance.

After completion of the Phase 1/2 study, Mezzion Pharma Co. Ltd continued its partnership with the PHN to create and execute the FUEL study. This 400-patient, double-blind, placebo-controlled trial is the largest medication trial ever undertaken for those with any form of congenital heart disease and was conducted to determine the safety and efficacy of daily oral therapy with udenafil in adolescents with single ventricle heart disease who had undergone Fontan palliation. The primary aim was to determine the effect of udenafil on exercise performance over a 26-week treatment period. Safety was evaluated throughout the 26-week period and for up to an additional 3 months. Mezzion Pharma Co. Ltd and the PHN are also conducting an open-label extension trial to continue to evaluate the tolerability and safety of udenafil over an additional 3-year time period.

8 Study Objectives

The primary objective of the study was to evaluate the effect of 26 weeks of treatment with udenafil (87.5 mg, BID) on exercise capacity in adolescents with Fontan physiology.

The secondary objectives of this study of adolescents with Fontan physiology were to:

- Determine the effect of 26 weeks of treatment with udenafil on echocardiographic indices of systolic and diastolic ventricular performance.
- Determine the effect of 26 weeks of treatment with udenafil on endothelial function.
- Evaluate the effect of 26 weeks of treatment with udenafil on serum brain natriuretic peptide (BNP) level, a biomarker of heart failure.
- Evaluate the safety of udenafil when given over a 26-week time period.
- Determine if 26 weeks' treatment with udenafil alters functional health status.
- Establish a collection of genetic material to identify genetic determinants of exercise capacity and response to udenafil and for unspecified future studies.
- Determine the prevalence and severity of complications, including protein-losing enteropathy, plastic bronchitis, hospitalizations, cardiac transplantation and death in adolescents who received udenafil.
- Explore the impact of udenafil on atrial and ventricular premature beats and arrhythmia burden.

9 Investigational Plan

9.1 Overall Study Design and Plan Description

This was a Phase 3 randomized, placebo-controlled, double-blind, 26-week, multicenter study of the effects of udenafil versus placebo in adolescents with Fontan physiology. The target sample size was 400 adolescents (200 per treatment group).

At PHN sites, potential subjects were identified through a screening chart review. Subjects who met initial study eligibility criteria, were receiving primary cardiac care at the PHN site, and were geographically local to the PHN site were approached regarding participation. In

addition, auxiliary sites in the United States and Korea were recruited at the beginning of the study to augment the number of potential subjects.

Subjects who agreed to participate had baseline testing performed to determine eligibility with inclusion/exclusion criteria. Subjects performed an exercise test to maximal effort to be eligible for randomization and study drug initiation. A subject who was unable to achieve a maximal effort (respiratory exchange ratio [RER] ≥1.10) on exercise testing but who otherwise qualified for inclusion, was offered the opportunity to repeat the test within 2 weeks of time of consent. Subjects with maximal minute oxygen consumption (VO_2) <50% of predicted for age and gender, based on their most recent prior clinical exercise test, were excluded from the study.

Eligible subjects were stratified by ventricular morphology (single left vs single right or mixed) and randomly assigned by a web-based system at the data coordinating center (DCC) to 1 of 2 treatment groups: orally administered udenafil (87.5 mg BID) or matching placebo BID. The first dose of randomized study drug was administered at the clinic (Visit 1, baseline).

Approximately 2 hours (± 30 minutes) post dosing, resting heart rate and blood pressure were measured, and the subject performed a self-limited 6-minute walk. A repeat heart rate and blood pressure were measured immediately following and approximately 2 hours (± 30 minutes) following the 6-minute walk. Subjects who had a drop in systolic blood pressure >20 mmHg from the pre- to post-6-minute walk measurement, or had a drop in systolic blood pressure below the 5th percentile for age, were excluded from receiving any further study drug. Continuing subjects were dispensed their initial supply of study medication and instructed to take 1 tablet orally BID.

Subjects returned to the clinic at Week 26 (study completion/early termination). In addition to clinic visits, study coordinators contacted each subject by telephone the day after the baseline visit to discuss any adverse events (AEs). Subjects were also contacted by telephone at Weeks 1, 2, 3, 4, 8, 13, 17, and 21 to ensure the study drug was well tolerated, to monitor study drug adherence, record AEs and concomitant medications, and offer pregnancy counseling, if needed. Subjects were encouraged to notify the study coordinator between scheduled contact dates with any new onset symptoms or complications.

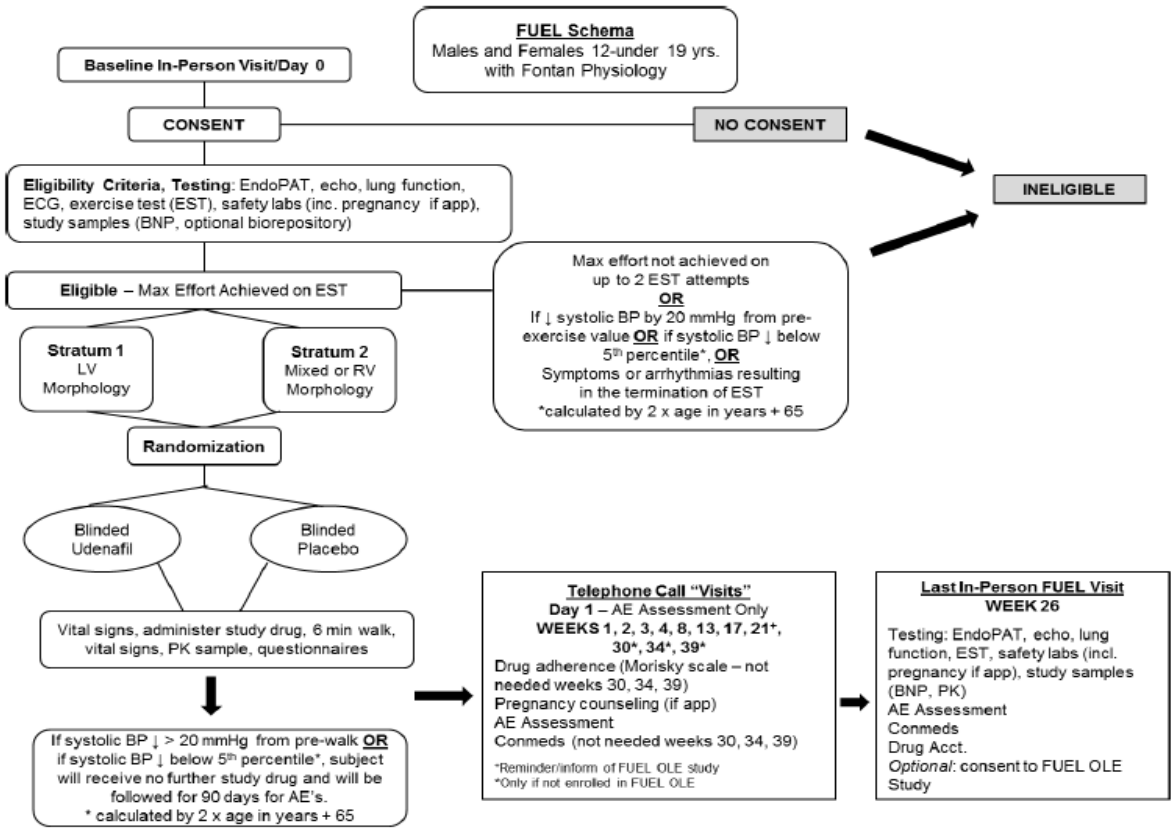
In-clinic study visits included assessments of safety (AEs, concomitant medication use, vital signs, and clinical safety laboratory evaluations), efficacy (exercise testing, echocardiogram, EndoPAT®, BNP, and quality of life measurements), and PK.

The duration of study drug dosing was 26 weeks. When an individual subject completed the study, the subject's primary cardiologist was notified, and the study drug was stopped. All subjects were invited to participate in an open-label, 12-month safety extension study of udenafil. Any subject declining participation in the extension study was to be followed for 90 days at Weeks 30, 34, and 39 for any additional AEs.

Subjects were given the opportunity to participate in the heart rhythm-monitoring subset of FUEL until a total of 25% of all randomized subjects had been included. Heart rhythm monitoring included a 7-day baseline monitor and a 3-day steady state monitor, as described in Section 9.5.1.2.6.

The study design is displayed in Figure 1. The overall schedule of assessments is provided in Table 2. Table 3 presents procedures performed before and after the first dose of study drug in the clinic at Visit 1.

Figure 1: Study Design



AE=adverse event; BNP=brain natriuretic peptide; BP=blood pressure; ECG=electrocardiogram; echo=echocardiogram; EST=exercise stress test; FUEL=**F**ontan **U**denafil **E**xercise **L**ongitudinal Assessment Trial; LV=left ventricular; min=minute; OLE=open-label extension; PK=pharmacokinetic; RV=right ventricular; yrs=years

9.2 Discussion of Study Design, Including the Choice of Control Groups

This was a Phase 3 randomized, placebo-controlled, double-blind, multicenter study. Randomized, double-blind controlled designs are standard to provide unbiased evaluations of study drug effects. Because there currently are no approved treatments for Fontan physiology, the use of a placebo control was considered ethical.

The dosage (87.5 mg) and frequency of administration (BID) of the study drug were determined by results of the recently completed PHN dose-escalation study of udenafil in adolescents with Fontan palliation (PHN-Udenafil-01).

Prior to randomization, eligible subjects were stratified by ventricular morphology (single left vs single right or mixed). The rationale for ventricular stratification was based on the results of previous PHN cross-sectional studies that demonstrated a weak but significant difference in certain resting echocardiographic and exercise results based on morphology (Paridon 2008; Anderson 2008). In addition, preliminary data on PDE-5 inhibitors suggested a difference in exercise performance based on morphology (Goldberg 2011).

9.3 Selection of Study Population

The target sample size was 400 male and female subjects with Fontan physiology who fulfilled all the eligibility criteria. A chart review was performed by the PHN core sites to determine potential subject availability. Potential subjects were identified as meeting study eligibility criteria, receiving primary cardiac care at the PHN site, and being geographically local to the PHN site.

9.3.1 Inclusion Criteria

Only subjects who met all of the following criteria were included:

1. Males and females with Fontan physiology who were 12 to less than 19 years of age at enrollment.

2. Participant consent or parental/guardian consent and participant assent.

3. Participant fluent in English, Spanish, or Korean.

4. Current anti-platelet or anticoagulant therapy.

9.3.2 Exclusion Criteria

Subjects were excluded if they met any of the following criteria:

1. Weight <40 kg.
2. Height <132 cm.
3. Hospitalization for acute decompensated heart failure within the last 12 months.
4. Current intravenous inotropic drugs.
5. Undergoing evaluation for heart transplantation or listed for transplantation.
6. Diagnosis of active protein-losing enteropathy or plastic bronchitis within the last 3 years or a history of liver cirrhosis.
7. Known Fontan baffle obstruction, branch pulmonary artery stenosis, or pulmonary vein stenosis resulting in a mean gradient of >4 mmHg between the regions proximal and distal to the obstruction as measured by either catheterization or echocardiography, obtained prior to screening for the study.
8. Single lung physiology with greater than 80% flow to one lung.
9. Maximal VO_2 less than 50% of predicted for age and gender at enrollment.
10. Severe ventricular dysfunction assessed qualitatively by clinical echocardiography within 6 months prior to enrollment.
11. Severe valvar regurgitation, ventricular outflow obstruction, or aortic arch obstruction assessed by clinical echocardiography within 6 months prior to enrollment.
12. Significant renal (serum creatinine >2.0 mg/dL), hepatic (serum aspartate aminotransferase and/or alanine aminotransferase >3 times upper limit of normal), gastrointestinal or biliary disorders that could impair absorption, metabolism or excretion of orally administered medications, based on laboratory assessment 6 weeks prior to screening for the study.
13. Inability to complete exercise testing at baseline screening.
14. History of PDE-5 inhibitor use within 3 months before study onset.

15. History of any other medication for treatment of pulmonary hypertension within 3 months before study onset.

16. Known intolerance to oral udenafil.

17. Frequent use of medications or other substances that inhibit or induce cytochrome P450 (CYP)3A4.

18. Current use of alpha-blockers or nitrates.

19. Ongoing or planned participation in another research protocol that would either prevent successful completion of planned study testing or invalidate its results.

20. Noncardiac medical, psychiatric, and/or social disorder that would prevent successful completion of planned study testing or would invalidate its results.

21. Cardiac care, ongoing or planned, at a non-study center that would impede study completion.

22. For females: Pregnancy at the time of screening, pregnancy planned before study completion, or refusal to use an acceptable method of contraception for study duration if sexually active.

23. Unable to abstain or limit intake of grapefruit juice during the duration of the study.

24. Refusal to provide written informed consent/assent.

25. In the opinion of the primary care physician, the subject was likely to be noncompliant with the study protocol.

26. History of clinically significant thromboembolic event, as adjudicated by study Investigators that may have put the subject at increased risk of a subsequent event while participating in the study.

9.3.3 Removal of Subjects from Therapy or Assessment

9.3.3.1 Discontinuation of Study Drug

Study drug could have been discontinued temporarily or permanently, but subjects were to remain in the study and complete all study data collection and follow-up measures, including

exercise performance testing. Study drug could have been discontinued for the following reasons:

- An adverse experience, including failure to tolerate study medication that, in the judgment of the Investigator or primary physician, required drug discontinuation.
- Voluntary discontinuation of study drug by the subject.
- Meeting withdrawal criteria following the 6-minute walk (see Section 9.1).

Per the Manual of Operations, the study drug was interrupted if the subjects needed to temporarily or permanently discontinue current anti-platelet or anticoagulant therapy. If the interruption was temporary, subjects were eligible to restart study drug with the resumption of anti-platelet or anticoagulant therapy.

Study drug was to be permanently discontinued for pregnancy, anaphylactic reaction, serious side effects including persistent hypotension, visual changes, or priapism that did not respond to temporary discontinuation of the study drug, and if deemed necessary by the study Investigator or primary physician, either due to side effects or due to need for open-label drug administration of a PDE-5 inhibitor.

When possible, the subject was to undergo an exercise test, EndoPAT, and echocardiogram before permanent discontinuation of the study drug. All information regarding any temporary stop and restart of study drug was to be recorded.

9.3.3.2 Subject Withdrawal from the Trial

End-of-study testing was obtained whenever possible on subjects who withdrew early. The reason for withdrawal was to be documented for all subjects withdrawn from the study. A subject could have been withdrawn from study participation for the following reasons:

- Subject (or legal guardian) declined further study participation.
- Lost to follow-up despite repeated, multiple attempts by the site Investigator and study coordinators to contact the subject.
- In the Investigator’s or other physician’s judgment, it was in the subject’s best interest.

If the subject refused to continue with the study visits, every attempt was made to continue contact by telephone, written communication, or record review to determine if outcome events (death, hospitalizations and major complications) had occurred, unless the subject specifically refused such follow-up. If the withdrawing subject was unwilling to have his/her medical records reviewed until the end of the study period (to document vital status and cause of death), he/she must have submitted a written refusal.

9.4 Treatments

9.4.1 Treatments Administered

Subjects were randomized to receive either oral udenafil (87.5 mg BID) or matching placebo BID for 26 weeks.

9.4.2 Identity of Investigational Product(s)

9.4.2.1 Study Drug

A description of study drug is provided below.

Dosage form description	Pale-orange, oval-shaped, film-coated tablets of 87.5 mg udenafil or matching placebo (0 mg drug). Tablet inactive ingredients: lactose monohydrate, corn starch, low substituted hydroxypropyl cellulose, hydroxypropyl cellulose, talc, magnesium stearate, colloidal silicon dioxide, hydroxypropyl methylcellulose, titanium dioxide, FD&C Yellow No. 6 Aluminum Lake, and iron oxide red.
Package description	One plastic bottle of 60 tablets per bottle.
Manufacturer	Dr. Reddy's Laboratories Ltd., FTO-3, Bachupally, Hyderabad, India.
Dosage per time unit	One tablet orally twice a day.
Storage	Udenafil tablets were to be stored at 20°C to 25°C (68°F to 77°F); excursions were permitted to 15°C to 30°C (59°F to 86°F). The study drug must have been protected from unauthorized access (eg, in a locked storage facility). Any unused, partially used, or empty bottles of study drug were destroyed at the site at the time of the site's close-out visit. Destruction of the study drug was properly documented on forms provided by the Sponsor or designee.
Batch number	UDBT15-10 (udenafil); P1MT15-09 (placebo to match udenafil)

Subjects receiving each batch of study drug are identified in Appendix 16.1.6.

9.4.2.2 Labelling

The labels of the investigational product contained the following information:

• Name and address of the Sponsor
• Product name
• Mode of administration
• Protocol identification and name
• Subject number
• Quantity and bottle number
• Storage conditions
• “Caution: New Drug – Limited by Federal Law to Investigational Use”

The composition, pharmaceutical quality, batch number, and expiration date of the investigational (test) product were traceable via the bottle number.

9.4.2.3 Accountability

The Site Principal Investigator had overall responsibility for the use of the study drug. The Site Principal Investigator or designee confirmed receipt of the study drug by signature and date, and returned a duplicate copy of receipt to the Sponsor or designee.

Under no circumstances was the Investigator to allow the investigational drugs to be used other than as directed by the protocol. Qualified study personnel used the specified randomization system to assign subjects to treatment and maintained accurate study drug-dispensing records regarding the date and amount dispensed to each subject. Reasons for digression from the expected dispensing regimen were to be recorded. The study drug inventory record was available for inspection by representatives of the Sponsor and was subject to regional regulatory authority inspection at any time. At the conclusion of the study, the Site Principal Investigator provided a copy of this record to the Sponsor.

9.4.3 Method of Assigning Subjects to Treatment Groups

Randomization assignments were generated by a web-based system at the DCC, after confirmation of study eligibility. Eligible subjects were stratified by ventricular morphology (single left vs single right or mixed) and randomly assigned to udenafil or placebo.

The randomization codes and treatment assignments by subject number are provided in Appendix 16.1.7.

9.4.4 Selection of Doses in the Study

The dosage and frequency of administration of the study drug were determined by the Phase 1/2 dose-escalation study of udenafil in adolescents with Fontan palliation completed by the PHN (PHN-Udenafil-01). Statistically significant improvement in exercise capacity or vascular function could not be determined in this very small study. However, oral administration of 175 mg/day udenafil (87.5 mg BID) for 5 days improved ventricular performance as measured by blood pool myocardial performance index (MPI). Thus, subjects in the current study took udenafil 87.5 mg BID or matching placebo BID.

9.4.5 Selection and Timing of Dose for Each Subject

Subjects were instructed to take the study drug twice a day. To minimize any potential diurnal and/or PK effect, the time of administration of the study drug at baseline and Week 26 was to match.

9.4.6 Blinding

The study drug and the placebo were identical in appearance to assure blinding of study drug. The randomization assignment was seen only by the statistician at the DCC and was not available to the family/subject, study coordinator, investigators, or personnel administering study procedures. The exercise testing laboratories and echocardiogram core laboratory were blinded to group assignment and study visit. All remained blinded as to treatment group assignment until after all study data were analyzed.

In rare life-threatening or emergency situations, when the identity of the study drug must have been known to the Investigator in order to provide appropriate medical treatment or if required to assure safety of study participants, an emergency code break could have been requested from the site research pharmacist after full discussion with the PHN Center Primary Investigator. If the code break for a subject was required, the DCC must have been informed within 1 working day of the event. The reason for breaking the code must have been documented in an appropriate eCRF, along with the date and the initials of the person who broke the code.

9.4.7 Prior and Concomitant Therapy

Subjects were to be treated with other medications at the discretion of their physicians. Management could have been symptomatic treatment (eg, hypotension from overdose or other cause) or observation and monitoring (eg, priapism). At study visits, current

medications were recorded on the study forms. If a subject began open-label use of any PDE-5 inhibitor at any time during the study, withdrawal from study drug was required. The following drug interactions have been observed with PDE-5 inhibitors including udenafil:

- Medications or other substances that strongly inhibit CYP3A4 including, but not limited to, erythromycin, indinavir, nelfinavir, clarithromycin, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole, and nefazodone.
- Medications or substances that strongly induce CYP3A4 including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort.
- Alpha blockers
- Intravenous inotropic drugs
- Bosentan
- Ritonavir
- Medications with a drug interaction that were to be avoided:
    - Boceprevir
    - PDE-5 inhibitors including sildenafil
    - Telaprevir
    - Vasodilator (organic nitrates) including isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin
    - Soluble guanylate cyclase stimulators
- Select antihypertensives including amlodipine, angiotensin II receptor blockers, enalapril, and metoprolol were to be used with caution, as small decreases in blood pressure occurred when udenafil was co-administered with these agents.

Grapefruit juice was to be limited or avoided throughout study participation, as it may increase serum levels and/or the toxicity of udenafil. In preparation for EndoPAT testing, subjects were required to abstain from caffeine and to have fasted for 8 hours prior to testing.

9.4.8 Treatment Compliance

Study drug adherence was assessed at each in-person study visit by comparing the expected versus actual consumption of study drug tablets. Return of study drug bottles coincided with scheduled monthly monitoring calls. During each call contact, the study coordinator reminded the subject to return study drug bottles to the site. The study coordinator or pharmacist measured and recorded the number of remaining tablets, and a study drug supply was dispensed as required. Self-report of study drug compliance was assessed with administration of the Morisky scale during each call contact. The Morisky scale is a questionnaire used to predict adherence to medication therapies (Morisky 1986).

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

The overall schedule of assessments is provided in Table 2. Table 3 presents procedures performed before and after the first dose of study drug in the clinic at Visit 1.

Table 2: Study Assessments and Procedures

Number and Type	Visit 1	Call 1	Calls 2-6	Call 7	Calls 8-9	Visit 2	Calls 10-12
Time point	**Screening/ Baseline Day 0[a]**	**Day 1**	**Weeks 1, 2, 3, 4, 8**	**Week 13**	**Weeks 17, 21**	**Week 26**	**Weeks 30, 34, 39**
Visit Windows			**± 3 days**	**± 10 days**	**± 3 days**	**± 10 days**	**± 10 days**
Type of Visit	**In person**	**Call**	**Call**	**Call**	**Call**	**In person**	**Call**
Informed consent/assent	X						
Assign subject identification number	X						
Inclusion/exclusion criteria	X						
Physical examination	X					X	
Medical history	X						
Demographic data	X						
Prior/concomitant medications	X		X	X	X	X	
EndoPAT® vascular assessment	X					X	
Serum/urine pregnancy test (females only)	X					X	
Clinical laboratory tests (creatinine, ALT, AST)	X					X[b]	
Biomarker (BNP) sample	X					X	
Genetic repository sample (optional)	X					X[c]	
Pharmacokinetic sample	X[b]					X[b]	
Echocardiogram	X					X	
Exercise testing	X[d]					X	
Randomization	X						
Dispense study drug	X						
Vital signs (resting BP and HR)	X					X	
Administer first study drug dose in clinic (Table 3)	X						
PedsQL generic/cardiac modules; PCQLI; HAES	X					X	
Perform drug accountability	X					X	
Pregnancy counseling (if applicable)	X		X	X	X	X	
Adverse events assessment	X	X	X	X	X	X	X
Morisky Scale (MMAS)			X	X	X		
Schedule/confirm next visit	X	X	X	X	X	X	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=brain natriuretic peptide; BP=blood pressure; HAES=Habitual Activity Estimation Scale; HR=heart rate; MMAS=Morisky Medication Adherence Scale; PCQLI=Pediatric Cardiac Quality of Life Inventory; PedsQL=Pediatric Quality of Life Inventory

a Baseline visit could have been combined into a single day or split into 2 days as long as the duration of the time between the visits was no more than 7 days.

b At 2 hours post-dose.

c As applicable, if missed at baseline visit.

d If a subject failed the first exercise test at the baseline visit, he/she was not randomized. At the baseline and Week 26 visits, at the site Investigator's discretion, the exercise test may have been repeated within 14 days. If a second exercise test was needed, the urine (or blood) pregnancy test must have been performed for eligibility (if applicable).

Table 3: Schedule of Procedures – Visit 1 (Before and After First Dose in the Clinic)

Procedure	Times from Administering First Dose of Study Medication			
	<1 hour prior to dose	**0 hour**	**2 hours ± 30 minutes**	**4 hours ± 30 minutes**
Vital signs (resting blood pressure and heart rate)	X			X (before discharge from clinic)
Administer first dose of study drug (one 87.5 mg tablet or matching placebo)		X		
Vital signs immediately before and following a 6-minute self-limiting walk			X	
Blood sample for determination of udenafil and metabolite concentration immediately after the 6-minute walk			X	
Record adverse events		X	X	X
Dispense initial study drug for home administration and discharge from clinic				X

9.5.1.1 Efficacy Assessments

9.5.1.1.1 Exercise Testing

Aerobic exercise performance was assessed by a cardiopulmonary exercise stress test (CPET) using a standard ramp cycle ergometry protocol and with the collection of expired gases (Paridon 2008). The ramp cycle protocol has been previously used in research studies of children and adults with congenital heart disease, including those with Fontan physiology (Anderson 2008; Paridon 2008).

The CPET was performed at Visit 1 (baseline) and at Week 26. The protocol consisted of sitting quietly on the ergometer for 3 minutes followed by 3 minutes of unloaded pedaling. The work rate was then increased using a ramp protocol with a slope chosen to achieve the subjects predicted maximal work rate in 10 to 12 minutes of total cycling time. A maximal aerobic effort was based on the RER (minute carbon dioxide production divided by minute oxygen consumption) at peak exercise equal to or greater than 1.10. All exercise stress test data were averaged over 10- or 20-second time intervals based on the specifications of the sites' metabolic carts.

Achieving a RER of equal or greater than 1.10 has been associated with a maximal aerobic effort, being an indicator of the respiratory compensation for the lactic acidosis that occurs

with a maximal aerobic effort. Use of the RER for this purpose has been well described in multiple studies of exercise with the Fontan procedure (Giardini 2008; Paridon 2008; Fernandes 2010). To ensure a high proportion of subjects achieve a maximal effort on both the baseline and Week 26 exercise studies, subjects who failed to achieve a RER of 1.10 or higher were offered an opportunity to perform a second exercise test within 2 weeks of the failed test.

Pulmonary function testing, electrocardiograms, blood pressure, pulse oximetry, and metabolic rates were monitored during exercise testing. The CPET protocol is described in Protocol Section 18.1.

A test data review plan was implemented after all exercise testing was completed. In an effort to reduce measurement variability, all exercise stress test interpretations were to be reviewed by blinded exercise physiologists with specific expertise in the exercise protocol used in this study. Results from the metabolic cart containing the original exercise test record (or paper/electronic copy if original record was not available) at baseline and Week 26 were reviewed and compared to the local interpretation. Final data represent a consensus between the exercise physiologists and local personnel from the exercise laboratory.

9.5.1.1.2 Echocardiogram

A focused echocardiogram was performed at Visit 1 (baseline/pre-treatment) and at Week 26 to evaluate systemic ventricular volume, eccentricity, systolic and diastolic function, and severity of atrioventricular valve regurgitation.

The change in the MPI from baseline to Week 26 was determined by velocities obtained from blood pool Doppler assessment of the inflow and outflow tract of the dominant ventricle.

9.5.1.1.3 Endothelial Function

EndoPAT 2000 measurements were performed at Visit 1 (baseline) and at Week 26. Endothelial function was assessed via changes in EndoPAT2000®-derived measures of reactive hyperemia index (RHI), markers of endothelial function, and augmentation index, a marker of arterial stiffness.

9.5.1.1.4 Biomarker: Brain Natriuretic Peptide

The serum level of BNP was assessed in blood samples collected at Visit 1 (baseline) and at Week 26. Measurements of BNP were performed at the central laboratory.

9.5.1.1.5 Quality of Life and Functional Health Status

Quality of life and functional status were measured with the Pediatric Quality of Life Inventory (PedsQL; self-report version), PedsQL Cardiac Module, and the Pediatric Cardiac Quality of Life Inventory (PCQLI) instruments. Domains of primary interest from the PedsQL were the Physical Functioning score and the Psychosocial Functioning score.

The PedsQL is a short questionnaire, has been used in multiple studies and has normal values, has a cardiac-specific module, has both parent and subject versions, and spans ages into adulthood (Varni 2001; Varni 2005; Varni 2009). It has been used in a previous study of Fontan subjects (Manlhiot 2009).

The PCQLI is a congenital heart disease-specific instrument that has shown good validity, has both parent and subject versions, and spans ages up to 18 years (Marino 2008; Marino 2010; Marino 2011).

9.5.1.2 Safety Assessments

Safety was assessed by monitoring AEs, vital signs, clinical laboratory test results, and physical examinations. Optional heart rhythm-monitoring was performed for a subset of subjects.

The Data and Safety Monitoring Plan for this study followed standard PHN monitoring principles. Oversight of data and safety was provided by the PHN DSMB, appointed by the NHLBI.

9.5.1.2.1 Adverse Events

An AE was defined as any untoward (eg, unfavorable, negative, or harmful) medical occurrence associated with the use of a drug in humans, whether or not the event was considered drug related. An event could have been any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the product.

Adverse events were classified as to seriousness (serious, not serious), expectedness (expected, unexpected), and potential relationship to the study drugs (not related, possibly related, probably related). For AEs with a causal relationship to the study drug, follow-up by the Investigator was required until the event or its sequelae resolved or stabilized at a level acceptable to the Investigator.

All AEs unresolved at the time of the subject's termination from the study were to be followed by the Investigators until the events were resolved, the subject was lost to follow-up, or the AE was otherwise explained or had stabilized. Any death or other serious adverse event (SAE) that may have been related to the study drugs and that occurred at any time after a subject had discontinued study drug or terminated study participation was to be reported.

An SAE was one that:

- Resulted in death,
- Was life-threatening (the subject was, in the view of the Principal Investigator, in immediate danger of death from the event as it occurred),
- Required inpatient hospitalization or prolongation of existing hospitalization,
- Resulted in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Was a congenital anomaly/birth defect in the offspring of a participant, or
- Was an important medical event that may have jeopardized the subject or required medical/surgical intervention to prevent one of the SAE outcomes.

An unexpected AE or adverse reaction was one for which the nature or severity was not consistent with information in the protocol, consent form, or product brochure. An AE was considered expected if it was known to be associated with the study drugs and/or the disease state.

Causality assessment was required to determine which events required expedited reporting.

- Not related: the event was clearly related to other factors, such as the subject’s clinical state or non-study drugs or interventions.
- Possibly related: the event followed a compatible temporal sequence from the time of administration of the study drug but could have been produced by other factors such as the subject’s clinical state or non-study drugs or interventions.
- Probably related: the event followed a reasonable temporal sequence from the time of drug administration and could not be reasonably explained by other factors such as the subject’s clinical state or non-study drugs or interventions.

The severity of AEs was categorized using the Common Terminology Criteria for Adverse Events Version 4.0 grades:

- 1 (mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- 2 (moderate): minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- 3 (severe): severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- 4 (life-threatening): life-threatening consequences; urgent intervention indicated.
- 5 (death): death related to AE.

Study Investigators reported all AEs, regardless of expectedness and relationship to study drug, to the DCC. The DSMB and NHLBI were assisted by an independent medical monitor in reviewing SAEs in PHN studies. The PHN medical monitor was the NHLBI's designee for determining causality and expectedness of all SAEs.

Serious AEs, including important medical events, were to be reported within 24 hours of first knowledge of the event; non-serious AEs were to be reported within 7 calendar days of first knowledge of the event. In addition, the site Investigator or designee was responsible for reporting all SAEs to the local IRB/REB in accordance with local policies and procedures.

9.5.1.2.2 Clinical Laboratory Tests

Blood samples were collected on the day of baseline testing and at Week 26 and consisted of serum creatinine, alanine aminotransferase, aspartate aminotransferase, and in females, serum or urine pregnancy test.

An optional blood sample was acquired from each subject once during the trial, preferably at study enrollment, to explore the genetic and pharmacogenetic determinants of exercise capacity, response to udenafil and other outcomes in Fontan patients. If blood collection was not possible, saliva was collected when feasible. The sample may be used for future studies.

9.5.1.2.3 Prior and Concomitant Medications

Prior and concomitant medications were collected at baseline. Concomitant medications were collected at visits from Week 1 through Week 26.

9.5.1.2.4 Physical Examinations

A limited physical examination was performed at baseline and Week 26.

9.5.1.2.5 Vital Signs

Vital signs (resting blood pressure and heart rate) were assessed at less than 1 hour prior to the first dose of study drug, 2 hours ± 30 minutes after the first dose of study drug, immediately after self-limited 6-minute walk, 4 hours ± 30 minutes after the first dose of study drug, and at Week 26.

9.5.1.2.6 Heart Rhythm Monitoring

For those subjects who opted to participate, heart rhythm monitoring included a 7-day baseline monitor and a 3-day steady-state monitor. The planned procedures for heart rhythm monitoring are described in Protocol PHN-Udenafil-02 (FUEL) Section 6.3.5. The number of subjects choosing to participate was too low for analysis of heart rhythm.

9.5.2 Appropriateness of Measurements

Studying the effect of any intervention in the Fontan population is difficult given the absence of readily measured, reliable and reproducible end points. Given the difficulty with hard endpoints, measures of exercise capacity are frequently used and accepted as surrogate endpoints for the purpose of measuring change over time or response to therapeutic intervention. Of the measures of aerobic exercise performance, maximal VO_2 has been shown to be a consistent and sensitive marker of deteriorating function, onset of symptoms of heart failure, and increasing risk for sudden death across a broad range of diagnostic categories of heart disease.

In studies of young adults with variable types of congenital heart disease, a maximal VO_2 of approximately 50% of predicted for age and gender appears to be the threshold value for increased risk of heart failure and death (Diller 2005; Canter 2007; Giardini 2007; Diller 2010). For those with a Fontan circulation, the PHN Fontan Cross-Sectional Study demonstrated a population maximal VO_2 of 66% of predicted normative values at the onset of adolescence while Giardini and colleagues have shown a predicted rate of decline of up to

2.6% per year. Taken together, these data suggest that the population would fall below the 50% threshold early in the third decade of life. An intervention capable of improving the baseline or slowing the slope of decline would therefore have important functional ramifications for long-term outcomes.

While a good measure across heterogeneous forms of heart disease, the use of maximal VO_2 as a therapeutic endpoint does have challenges unique to the Fontan circulation. Due to the intrinsic limitations of pulmonary vasodilatory reserve, the Fontan circulation's ability to maintain adequate preload to the systemic ventricle at higher levels of exercise is limited and can only be accomplished by prohibitively high CVPs. Under these circumstances, the ability to perform sub-maximal aerobic activity may be better preserved than maximal VO_2. The data from the PHN Fontan Cross-Sectional Study as well as additional studies support this notion (Paridon 2008; d'Udekem 2009; Goldstein 2010). Using Paridon 2008 as an example, VO_2 at ventilatory anaerobic threshold (VAT) was significantly better preserved at 78% of predicted compared to a maximal VO_2 at 66% of predicted.

The VO_2 at VAT measures the level of oxygen consumption at which one changes from aerobic to anaerobic activity, a clinically relevant level of exertion that is typical of what is encountered in routine volitional activity. For reasons discussed in detail in Section 11.4.7, VO_2 at VAT may be more appropriate than maximal VO_2 as an outcome measure for those with a single ventricle circulation. As is true for maximal VO_2, measurements of VO_2 at VAT also correlate with functional outcome. For this clinical study, VO_2 at VAT was chosen as a secondary exercise measure due to the technical challenge associated with obtaining measurements of the endpoint. Determination of VO_2 at VAT depends on each participant maintaining a consistent respiratory pattern over the duration of their exercise test. This is generally achievable by older adolescents and adults, but it may be less reliable in younger adolescents. However, as discussed in Section 11.4.7, our understanding of Fontan exercise physiology has evolved since the inception of this study and, even with the technical challenges, the importance of VO_2 at VAT as a critical surrogate endpoint for those who have undergone Fontan has become apparent.

Echocardiography is routinely and universally used to evaluate ventricular performance in serial follow-up of Fontan patients, a population known to have significant abnormalities in both ventricular systolic and diastolic function (Sano 1989; Frommelt 1991; Akagi 1993; Cheung 2000; Kaneko 2012). Animal studies have suggested that PDE-5 inhibitors may mitigate adverse remodeling in stressed myocardium, and previous single dose trials and pilot studies in those with a Fontan circulation have suggested an improvement in ventricular performance in response to treatment (Goldberg 2012; Tunks 2014; Van De Bruaene 2014;

Goldberg 2017; Garcia 2018). Given the importance of ventricular performance in the long-term health of those with all forms of heart disease, an improvement in this aspect of physiology would be of significant value across the population. The MPI is a measure of systolic and diastolic function that indexes isovolumetric relaxation and contraction times to the ventricular ejection time; a smaller number suggests more efficient contraction and relaxation. An improvement in MPI would be of benefit in this population, one with well documented abnormalities in systolic and diastolic function.

Studies have demonstrated a strong correlation between endothelial function and exercise capacity, including recent data utilizing EndoPAT in the assessment of endothelial function (Goldstein 2011; Goldstein 2016). Based on the known effect of PDE-5 inhibitors and the known endothelial dysfunction in the Fontan population (Mahle 2003; Inai 2004; Jin 2007; Binotto 2008), a measure of endothelial function is a useful candidate marker for a potential pharmacodynamic effect. The Framingham-modified RHI and raw RHI measures served as secondary outcome measures of vascular function.

Serum BNP is a useful biomarker in patients with heart failure from a variety of causes. A study of BNP levels in 510 patients after the Fontan procedure (median age 11.4 years) performed through the PHN revealed mean BNP levels of 25 ± 48 pg/mL (Atz 2011). Higher BNP was associated with several markers of suboptimal outcomes albeit with weak associations but may be a predictor of Fontan failure. In the pilot study by Goldberg, those with a serum BNP level >100 pg/mL had a more robust response to sildenafil (Goldberg 2011). Thus, BNP may be helpful in measuring a response to medical intervention.

The quality of life and functional status questionnaires have been widely used in multiple studies. The safety and PK measurements utilized were standard, widely used, and generally recognized as reliable, accurate, and relevant to the study population and study design.

9.5.3 Primary Efficacy Variable

The primary efficacy variable was the change in maximal VO_2 from baseline to Week 26 measured by cardiopulmonary exercise testing.

Secondary efficacy variables are listed in Section 9.7.1.4.2.

9.5.4 Drug Concentration Measurements

Immediately after completion of the 6-minute walk at Visit 1, approximately 2 mL of blood was obtained for determination of udenafil and metabolite concentrations. Another sample

was obtained at Week 26. Udenafil is primarily metabolized by the CYP3A4 and CYP3A5 enzymes in the liver. Therefore, udenafil levels can be influenced by variations in CYP3A4/5 genes that influence udenafil pharmacokinetics which, in turn, can influence the response to udenafil (Goldberg 2012; Shabanian 2013). The association of relevant variants with udenafil pharmacokinetics was to be assessed.

9.6 Data Quality Assurance

The DCC had the primary responsibility for all quality control and quality assurance activities for the study data. The DCC also required that each study site completed certain quality control activities, most of which were monitored by the DCC. Documentation of quality-assurance procedures are provided in Appendix 16.1.10.

The key quality control/quality assurance activities were as follows:

- Development of a Study Manual
- Preparation of clearly formatted and carefully constructed Data Forms with clear, up-to-date manuals of instruction
- Preparation of sign-off procedures for all eCRFs
- Provision of central protocol training and certification of all site data collection staff with the use of standardized checklists
- Provision of central e-Clinical Operating System (data management system) training and tracking of site personnel completing data entry and/or data management
- Verification of subject eligibility
- Provision of on-going monitoring of all protocol/data collection activities
- Inclusion of repeat measurements, as feasible, in the course of the study
- Provision of monitoring visits to sites as required with pre-specified goals and/or remote monitoring activities.

Review of central laboratory-related reports was conducted at least monthly to identify overall or site-specific problems in data or specimen acquisition and reporting of results.

The Sponsor contracted Advanced Clinical Services to audit the top enrolling sites and audit certificates were issued for these sites.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

The statistical methods described below are summarized from the final Statistical Analysis Plan (SAP), dated 23 June 2016. Changes from the planned analyses in the protocol that were specified in the final SAP are described in Section 9.8.2.

Formal hypothesis testing was performed only for the primary efficacy endpoint. All statistical tests were at the 0.05 alpha level, 2-tailed, unless stated otherwise. Descriptive statistics for categorical endpoints included the number and percent of subjects in each treatment group and category. Quantitative endpoints were summarized for each treatment group with the mean, median, standard deviation, minimum value, and maximum value. Individual subject data were presented in data listings that included normal reference ranges when appropriate.

9.7.1.1 Analysis Populations

Three analysis populations were defined:

- Intent-to-treat (ITT) population: The ITT population included all randomized subjects and was the primary population for efficacy analyses. Treatment assignments were analyzed according to the randomized treatment assignment.

- Safety population: The Safety population included all subjects who took at least 1 dose of randomized study drug and was the primary population for safety analyses. If the wrong study drug was administered (eg, subject was randomized to udenafil but received placebo), treatment assignment was analyzed according to the actual study drug received.

- Per Protocol population: The Per Protocol population included all subjects in the Safety population who met all entry criteria or, if criteria were not met, were granted a waiver by the Sponsor. Subjects with major protocol deviations were excluded (including subjects who received the wrong study drug). The Per Protocol population was used for sensitivity analyses of the primary efficacy endpoint.

9.7.1.2 Accountability and Protocol Deviations

Screening failures (ie, subjects who were not randomized) were summarized by the number and percentage of failures for each primary reason. The number and percent of subjects who were randomized, treated with randomized study drug, prematurely discontinued, and completed the study were summarized by treatment group. The number and percent of subjects were summarized by treatment group for each reason for premature discontinuation. For subjects who completed the study, the number of subjects who continued into the extension study were summarized.

The number and percent of enrolled subjects were summarized by study site, and the number of subjects included in each analysis population were summarized by treatment group.

Major protocol deviations were identified prior to breaking the blind. Deviations could have included, but were not limited to, departure from inclusion/exclusion criteria, received the wrong study drug, failure to perform the required assessments at specified time points, and scheduling of visits not in accordance with specifications.

9.7.1.3 Demographic and Baseline Characteristics

Demographic (eg, age, gender, race) and baseline characteristics were summarized descriptively for the Safety and ITT populations, for all subjects and for each treatment group. Medical and surgical history/physical findings were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with abnormalities in medical and surgical histories in each system organ class and preferred term were summarized for all subjects and by treatment group for the Safety population.

9.7.1.4 Efficacy Analyses

9.7.1.4.1 Primary Efficacy Endpoint

The treatment group difference for change in aerobic exercise performance (as measured by VO_2 at maximum exercise effort [maximal VO_2]) from baseline to Week 26 was assessed with an analysis of covariance (ANCOVA) with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline maximal VO_2.

Sensitivity analyses included:

- Primary efficacy analysis performed for the Per Protocol Population.
- ANCOVA model to assess treatment group differences in ranked changes of maximal VO_2 for the ITT and Per Protocol Populations.

9.7.1.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints included change from baseline to Week 26 in:

- Exercise capacity
    - VO_2 at VAT
    - Ventilatory equivalents of carbon dioxide (VE/VCO_2) at VAT
    - Respiratory rate and minute ventilation at peak exercise
    - Maximal work rate
    - Work rate at VAT
- Ventricular performance
    - MPI determined by velocities obtained from blood pool Doppler assessment of the inflow and outflow tract of the dominant ventricle. It is the primary ventricular performance endpoint of the echocardiogram.
    - Ventricular cavity size, eccentricity, and mass (based on echocardiogram)
    - Systolic function estimate using mean derivative of pressure over time during isovolumetric contraction and peak systolic annular velocity (S') on tissue Doppler
    - Qualitative and quantitative estimate of atrioventricular valve insufficiency
- Endothelial function: log-transformed reactive hyperemia index (lnRHI), as measured by pulse amplitude tonometry (PAT) testing using the EndoPAT device
- Natural logarithm transformation of BNP

- Functional health status, as measured by the full scale PedsQL
    - Physical functioning score
    - Psychosocial functioning score
    - Cardiac-specific quality-of-life score
- PCQLI score

Each secondary efficacy endpoint was summarized descriptively by treatment group.

Treatment group differences for endpoints associated with the PedsQL and PCQLI were to be assessed with Friedman's test using ventricular morphology (single left versus single right or mixed) as the stratification factor. The treatment group difference for the qualitative estimate of atrioventricular valve insufficiency was to be assessed with a Cochran-Mantel-Haenszel test using ventricular morphology (single left versus single right or mixed) as the stratification factor.

The remaining secondary efficacy endpoints were analyzed with the ANCOVA model with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a covariate for the baseline value.

9.7.1.4.3 Subgroup Analyses

Treatment group differences for the primary efficacy endpoint were summarized descriptively for the following subpopulations based on the following baseline characteristics:

- Gender (male, female)
- Race (Asian, African American, Caucasian, other)
- Ethnicity (Hispanic, non-Hispanic)
- Ventricular morphology (single left, single right, mixed)
- Age at Fontan surgery (<3 years vs ≥3 years)
- Baseline serum BNP level (<median, ≥median)
- Percent of predicted maximal VO_2 at baseline (<75%, ≥75%)

A 95% confidence interval of the difference in treatment group means was provided within each subpopulation.

9.7.1.4.4 Missing Data

The following imputation method was used for the primary analysis of the primary outcome:

- Subjects who had died or dropped out of the study with unknown vital status were to be assigned a maximal VO_2 of zero at Week 26. No subjects met this criterion.
- Subjects who were known to be alive, but who discontinued from the study (and were missing maximal VO_2 at Week 26) were assigned the latest value available.
- Subjects who completed Week 26, but were physically unable to reach maximum effort in cardiopulmonary exercise testing after 2 attempts, were assigned their baseline value (ie, zero change).

Two additional analyses to assess the impact of missing data were conducted as follows:

- Subjects with missing maximal VO_2 at Visit 4 were assigned a maximal VO_2 of zero.
- Subjects with missing maximal VO_2 at Visit 4 were excluded from analysis (ie, observed cases analysis).

Missing item scores for rating scales were imputed according to published methodology for the scale. Otherwise, missing data were not estimated for secondary efficacy endpoints.

9.7.1.5 Safety Evaluations

Safety assessments were summarized for the Safety population. No formal hypothesis testing was performed.

9.7.1.5.1 Extent of Exposure

The number of days from first to last dose was summarized descriptively for each treatment group. Percent compliance for the entire study was calculated as follows:

Number tablets missed = (number returned – (2 × number of days off study))

Number tablets expected = 2 × number of days on study

Percent Compliance = (1 - (number missed / number expected)) × 100.

A subject was considered on-study from Visit 1 until study completion or premature discontinuation of study drug. Percent compliance was summarized descriptively for each treatment group.

9.7.1.5.2 Adverse Events

All AEs were classified by the MedDRA with respect to system organ class and preferred term. The number and proportion of subjects who experienced treatment-emergent adverse events (TEAEs), defined as events that began after receipt of randomized study drug, were summarized by treatment group for the following:

- By system organ class and preferred term
- By intensity (mild, moderate, or severe/life threatening/death), system organ class, and preferred term
- By relationship to study drug (not related or related), system organ class, and preferred term
- By weight tertile, system organ class, and preferred term
- By age tertile, system organ class, and preferred term
- SAEs by system organ class and preferred term
- SAEs by relationship to study drug (not related or related), system organ class, and preferred term
- SAEs by weight tertile, system organ class, and preferred term
- SAEs by age tertile, system organ class, and preferred term
- AEs resulting in discontinuation of study drug by system organ class and preferred term

The number and percent of subjects reporting at least 1 TEAE of hypotension (eg, blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, hypotension, procedural hypotension), loss of consciousness, dizziness (eg, dizziness, dizziness exertional, procedural dizziness), presyncope, or syncope (syncope, syncope vasovagal) and the number and percent of subjects reporting each of the listed preferred

terms were summarized by treatment group. The 2 summaries were repeated by age tertiles and weight tertiles.

The number and percent of subjects reporting at least 1 TEAE of death, hospitalization for heart failure, or transplant and the number and percent of subjects reporting each of the listed preferred terms were summarized by treatment group. The 2 summaries were repeated by age tertiles and weight tertiles.

9.7.1.5.3 Clinical Laboratory Tests

Laboratory values were converted to the project-defined unit of measurement before analysis. Clinical laboratory variables were presented in 2 ways. First, change from baseline to Week 26 (study completion) was summarized descriptively for each treatment group. The baseline value was defined as the last assessment on or before dosing at Visit 1. Second, the number and proportion of subjects with treatment-emergent abnormal laboratory values were tabulated and the subjects identified. Treatment-emergent abnormal laboratory tests were those in which the baseline value was within the laboratory normal reference range and the postbaseline value was abnormal (ie, met Grade III or Grade IV toxicity criteria from the National Cancer Institute Common Terminology Criteria). All laboratory values obtained after Visit 1 were included in the analysis.

9.7.1.5.4 Vital Signs

Change from baseline (last vital sign value before the first dose of study drug at Visit 1) to each scheduled assessment was summarized descriptively by treatment group for each vital sign variable. Vital signs that were potentially clinically significant were identified according to prespecified criteria (listed in the SAP) and summarized descriptively by treatment group.

9.7.1.5.5 Prior and Concomitant Medications

The Concomitant Medications World Health Organization drug dictionary was used to classify all medications with respect to the Anatomical-Therapeutic-Chemical classification and preferred drug name. Prior and concomitant drug usage was summarized by Anatomical-Therapeutic-Chemical level 3 and preferred drug name. Medications with a start date before the first dose of study drug were considered prior medications. Medications with a stop date after the first dose of study drug or ongoing at study completion/discontinuation were considered concomitant medications. Therefore, medications that started before the study and continued into the study were counted as both prior and concomitant medications.

9.7.2 Determination of Sample Size

A sample size of 198 subjects per group would provide 90% power to detect a mean treatment group difference in change from baseline to Week 26 in maximal VO_2 scores of 10% (ie, an improvement of 2.8 mL/kg/min in the udenafil group compared to zero change in the control group, assuming a Type I error of 0.05 and standard deviation of 7.235). A difference of 2.8, equivalent to a 10% increase from a baseline of 28 mL/kg/min, represents approximately 0.4 standard deviations.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Changes in the Conduct of the Study

The original protocol, dated 09 March 2016, was amended 3 times. A copy of the final study protocol (Protocol PHN-Udenafil-02, dated 31 August 2017) is provided in Appendix 16.1.1.

Version 2 of the protocol (04 May 2016) included the following substantive modifications to the original protocol:

- Added a DSMB review of all data after the first 50 subjects had completed the study.
- Added the opportunity for subjects to enroll in a heart rhythm-monitoring subset of the FUEL study.

Version 3 of the protocol (30 May 2017) included the following substantive modifications to Version 2 of the protocol:

- Conversion of Visits 2 and 3 to telephone calls, removing vital sign measurements.

Version 4 of the protocol (31 August 2017) included the following substantive modifications to Version 3 of the protocol:

- Addition of inclusion criterion #4, which required potential participants to be on anti-platelet or anticoagulant therapy.
- Addition of exclusion criterion #26, which excluded potential participants if they had a history of clinically significant thromboembolic event.

9.8.2 Changes to Planned Analyses

9.8.2.1 Changes Between Protocol Finalization and Final Statistical Analysis Plan

The SAP was finalized 23 June 2016. Key changes to statistical analyses between protocol finalization and the final SAP are described below.

The protocol defined 2 non-ITT analysis populations. The SAP replaced these non-ITT analysis populations by defining the more traditional Per Protocol population. In addition, the SAP provided a definition for the Safety population.

The protocol stated that potential differential impact of continuous age on treatment outcomes would be assessed and that a treatment by subpopulation interaction test would be conducted to identify differential treatment effects. Tests for treatment by subpopulation were not performed due to the low power of the tests.

The protocol also stated that treatment group differences would be assessed within subpopulations if the interaction p-value was <0.10. These tests were not performed due to their potentially low power and bias due to lack of randomization within each subpopulation.

Minor clarifications were made to imputations for missing values.

Differences between the SAP and analyses presented in the clinical study report include:

- Presentation of the following for exercise capacity:
    - Percent predicted maximal VO_2
    - Heart rate at peak exercise
- Additional specific variables related to ventricular performance were summarized in the statistical tables.
- Friedman's test using ventricular morphology (single left versus single right or mixed) as the stratification factor was not used to assess treatment group differences for endpoints associated with the PedsQL and PCQLI. Differences were assessed using the same ANCOVA model as the other secondary endpoints.
- The qualitative estimate of atrioventricular valve insufficiency was not assessed.

- Subgroup analyses of AEs were also performed for gender, race, and ethnicity.
- Descriptive statistics of udenafil and metabolite concentrations were provided.

9.8.2.2 Changes Between Finalization of Statistical Analysis Plan and Blind Break

Key changes to statistical analyses between SAP finalization on 23 June 2016 and blind break on 19 July 2019 are described below.

Treatment group differences for the primary efficacy endpoint were summarized descriptively for subjects on afterload reducing agents in the study versus subjects who were not on afterload reducing agents in the study.

Analyses by visit were updated to account for protocol version 3, which replaced in-person Visits 2 and 3 (at Weeks 2 and 13, respectively) by telephone calls, and to remove collection of vital sign measurements at those time points.

9.8.2.3 Changes After Blind Break

Maximal VO_2 and VO_2 at VAT were summarized with units of mL/min in addition to the protocol-specified units of mL/kg/min. This was done since unchanged VO_2 in the presence of weight gain would cause VO_2 to appear to decrease when summarized as mL/kg/min.

Waterfall plots and cumulative distribution plots were generated for change from baseline to Week 26 in maximal VO_2 and VO_2 at VAT (mL/min and mL/mg/min).

Percent change from baseline was calculated for maximal VO_2 and VO_2 at VAT as the geometric mean ratio of the Week 26 minus baseline logarithm transformed exercise data.

An additional imputation method for missing data was included for exercise variables. When the Week 26 value was missing, the mean of non-missing Week 26 values (ignoring treatment group) was imputed.

For VO_2 at VAT, a linear regression model was also used to predict Week 26 VO_2 at VAT from Week 26 maximal VO_2. The predicted value from the model was used to impute VO_2 at VAT when maximal VO_2 was available; when maximal VO_2 was also missing, the average from all subjects with non-missing values was imputed.

Treatment-emergent abnormal laboratory tests were not identified on the basis of Grade III or Grade IV toxicity criteria from the National Cancer Institute Common Terminology Criteria. Shifts from within normal limits at baseline to above normal limits at Week 26 were summarized instead.

9.8.2.4 Changes to Address Refusal to File Letter

The MedDRA coding of some adverse events was revised for consistency per request by the Food and Drug Administration.

The definition of TEAEs was changed from events that began after receipt of randomized study drug to events that began after receipt of randomized study drug and within 90 days after last dose of study drug.

10 Study Subjects

10.1 Disposition of Subjects

A total of 976 subjects were screening failures. Of the 976 screening failures, 525 were ineligible, 407 did not provide informed consent, 21 were ineligible after informed consent, and 23 had no reason provided for screen failure (Table 14.1.1). Key study calendar dates for each subject are provided in Listing 16.2.8.5.

Subjects were enrolled at 30 study sites (26 United States, 2 Canada, 2 South Korea). Subject enrollment by site is summarized in Table 4.

Table 4: Subject Enrollment by Site

Site	Udenafil (N=200) n (%)	Placebo (N=200) n (%)	Total (N=400) n (%)
Hospital for Sick Children Toronto	4 (2.0)	8 (4.0)	12 (3.0)
Boston Children's Hospital	12 (6.0)	11 (5.5)	23 (5.8)
Columbia/CHONY	5 (2.5)	3 (1.5)	8 (2.0)
Children's Hospital of Philadelphia	20 (10.0)	22 (11.0)	42 (10.5)
Duke University Hospital	3 (1.5)	1 (0.5)	4 (1.0)
Medical University of South Carolina	9 (4.5)	4 (2.0)	13 (3.3)
University of Utah/Primary Children Medical Center	11 (5.5)	8 (4.0)	19 (4.8)
Children's Hospital of Los Angeles	5 (2.5)	5 (2.5)	10 (2.5)
Children's Hospital of Wisconsin	15 (7.5)	6 (3.0)	21 (5.3)
University of Michigan Health System, Ann Arbor	11 (5.5)	2 (1.0)	13 (3.3)
Cincinnati Children's Hospital Medical Center	13 (6.5)	17 (8.5)	30 (7.5)
Riley Children's Hospital Prairieland	3 (1.5)	4 (2.0)	7 (1.8)
Children's Hospital of Atlanta	9 (4.5)	12 (6.0)	21 (5.3)
Johns Hopkins All Children's Heart Institute	1 (0.5)	1 (0.5)	2 (0.5)
Washington University School of Medicine	1 (0.5)	4 (2.0)	5 (1.3)
Texas Children's Hospital	13 (6.5)	10 (5.0)	23 (5.8)
Alfred I. duPont Hospital for Children	3 (1.5)	7 (3.5)	10 (2.5)
Monroe Carrell Jr Children’s Hospital Vanderbilt	5 (2.5)	10 (5.0)	15 (3.8)
Seattle Children's Hospital	2 (1.0)	5 (2.5)	7 (1.8)
Cedars-Sinai Medical Center	3 (1.5)	1 (0.5)	4 (1.0)
Rady Children's Hospital, San Diego	4 (2.0)	2 (1.0)	6 (1.5)
Children's National Medical Center	4 (2.0)	4 (2.0)	8 (2.0)
Children's Mercy Hospital	5 (2.5)	8 (4.0)	13 (3.3)
Children's Hospital of Colorado Heart Institute	8 (4.0)	7 (3.5)	15 (3.8)
Phoenix Children's Hospital/Children's Heart Center	9 (4.5)	7 (3.5)	16 (4.0)
Children's Hospital & Medical Center - Omaha	2 (1.0)	7 (3.5)	9 (2.3)
Nationwide Children's Hospital	2 (1.0)	2 (1.0)	4 (1.0)
University of Alberta/Stollery Children’s Hospital	4 (2.0)	3 (1.5)	7 (1.8)
Seoul National University Children's Hospital	5 (2.5)	12 (6.0)	17 (4.3)
Sejong General Hospital	9 (4.5)	7 (3.5)	16 (4.0)

Source: Table 14.1.3
Program: T_14_1_3.sas

The percentage of subjects who discontinued study drug was low and similar between treatment groups (12 [6.0%] of udenafil-treated subjects, 9 [4.5%] of placebo-treated subjects). Six subjects (4 udenafil, 2 placebo) were prematurely discontinued from study drug

by physician decision and 11 subjects (6 udenafil, 5 placebo) were prematurely discontinued from study drug by subject (ie, participant) decision. Three udenafil-treated subjects discontinued study drug due to a serious TEAE and all other subjects discontinued study drug due to other reasons.

The profile of study discontinuations was similar to study drug discontinuations. Subject disposition is summarized in Table 5. Subjects who discontinued from study are identified in Listing 16.2.1, and subjects who discontinued study drug are identified in Listing 16.2.1.2.

Table 5: Subject Disposition

Disposition	Udenafil (N=200) n (%)	Placebo (N=200) n (%)	Total (N=400) n (%)
Randomized and treated	200 (100.0)	200 (100.0)	400 (100.0)
Prematurely discontinued study drug	12 (6.0)	9 (4.5)	21 (5.3)
Lost to follow-up	2 (1.0)	2 (1.0)	4 (1.0)
Physician decision to permanently stop drug	4 (2.0)	2 (1.0)	6 (1.5)
Due to serious TEAE	3 (1.5)	0	3 (0.8)
Due to other reasons	1 (0.5)	2 (1.0)	3 (0.8)
Participant decision to permanently stop drug	6 (3.0)	5 (2.5)	11 (2.8)
Due to other reasons	6 (3.0)	5 (2.5)	11 (2.8)
Discontinued study	12 (6.0)	6 (3.0)	18 (4.5)
Lost to follow-up	7 (3.5)	4 (2.0)	11 (2.8)
Physician decision to discontinue study	1 (0.5)	0	1 (0.3)
Due to serious TEAE	1 (0.5)	0	1 (0.3)
Due to other reasons	0	0	0
Subject decision to discontinue study	4 (2.0)	2 (1.0)	6 (1.5)
Due to other reasons	4 (2.0)	2 (1.0)	6 (1.5)
Completed study[a]	188 (94.0)	194 (97.0)	382 (95.5)
Continued in extension study	126 (63.0)	124 (62.0)	250 (62.5)

TEAE=treatment-emergent adverse event
a As defined by status change form
Source: Table 14.1.2
Program: T_14_1_2.sas

10.2 Protocol Deviations

The most frequent reasons for exclusion from the Per Protocol population included inability to complete exercise testing at baseline/screening (2 subjects), weight <40 kg (2 subjects), and any other deviations not listed under the defined categories (8 subjects).

Major protocol deviations are summarized in Table 6. Subjects with protocol deviations are identified in Listing 16.2.2.

Table 6: Major Protocol Deviations

Deviation	Udenafil (N=200) n (%)	Placebo (N=200) n (%)	Total (N=400) n (%)
Assessment compliance	1 (0.5)	0	1 (0.3)
Assessment not performed per protocol	1 (0.5)	0	1 (0.3)
Inclusion/exclusion compliance	3 (1.5)	1 (0.5)	4 (1.0)
Inability to complete exercise testing at baseline/screening	1 (0.5)	1 (0.5)	2 (0.5)
Weight <40 kg	2 (1.0)	0	2 (0.5)
Other compliance	3 (1.5)	5 (2.5)	8 (2.0)
Any other deviations not listed under the defined categories[a]	3 (1.5)	5 (2.5)	8 (2.0)
Study medication compliance	0	1 (0.5)	1 (0.3)

a Includes 7 subjects (3 udenafil, 4 placebo) at Riley Children's Hospital, where the data could not be verified as part of the on-site data cleaning project because the hard drive crashed and could not be recovered.
Source: Table 14.1.5
Program: t_14_1_5.sas

11 Efficacy Evaluation

11.1 Datasets Analyzed

No randomized subjects were excluded in the ITT and Safety populations. Approximately 97% of subjects in each treatment group were included in the Per Protocol population. Subjects excluded from the Per Protocol population are identified in Listing 16.2.3. The number and percentage of subjects in each analysis population are summarized in Table 7.

Table 7: Analysis Populations

Population	Udenafil (N=200) n (%)	Placebo (N=200) n (%)	Total (N=400) n (%)
Intent-to-Treat	200 (100.0)	200 (100.0)	400 (100.0)
Safety	200 (100.0)	200 (100.0)	400 (100.0)
Per Protocol	193 (96.5)	193 (96.5)	386 (96.5)

Source: Table 14.1.4
Program: T_14_1_4.sas

11.2 Demographic and other Baseline Characteristics

Most subjects were male (59.8%), white (81.0%), and not Hispanic or Latino (85.5%). Mean age at baseline was 15.5 years, with a range of 12.0 to 19.0 years. Demographic and baseline characteristics were similar between treatment groups. Demographic and baseline characteristics are summarized in Table 8.

Demographic and baseline characteristics of the ITT population (Table 14.1.6B) were identical to those of the Safety population (Table 14.1.6A). Demographic characteristics are provided by subject in Listing 16.2.4; weight and height are provided by subject in Listing 16.2.6.1.1.

Table 8: Demographic and Baseline Characteristics (Safety Population)

Demographic Characteristic	Udenafil (N=200)	Placebo (N=200)	Total (N=400)
Age (years)			
Mean (SD)	15.4 (2.033)	15.6 (1.978)	15.5 (2.005)
Median	15.43	15.40	15.41
Minimum, maximum	12.1, 19.0	12.0, 19.0	12.0, 19.0
Biological Gender, n (%)			
Female	89 (44.5)	72 (36.0)	161 (40.3)
Male	111 (55.5)	128 (64.0)	239 (59.8)
Race, n (%)			
White	169 (84.5)	155 (77.5)	324 (81.0)
Asian	17 (8.5)	21 (10.5)	38 (9.5)
Black or African-American	10 (5.0)	13 (6.5)	23 (5.8)
Multiple	2 (1.0)	2 (1.0)	4 (1.0)
Unknown	2 (1.0)	3 (1.5)	5 (1.3)
Not reported	0	6 (3.0)	6 (1.5)
Ethnicity, n (%)			
Hispanic or Latino	31 (15.5)	25 (12.5)	56 (14.0)
Not Hispanic or Latino	168 (84.0)	174 (87.0)	342 (85.5)
Unknown	1 (0.5)	1 (0.5)	2 (0.5)
Weight (kg)			
Mean (SD)	57.1 (13.925)	59.0 (13.187)	58.1 (13.577)
Median	53.45	57.00	55.65
Minimum, maximum	39.6, 123.0	40.0, 119.4	39.6, 123.0
Height (cm)			
Mean (SD)	162.5 (10.364)	164.7 (8.712)	163.6 (9.624)
Median	162.00	165.00	163.00
Minimum, maximum	139.8, 190.1	146.3, 190.8	139.8, 190.8

SD=standard deviation
Source: Table 14.1.6A
Program: T_14_1_6A.sas

Single ventricle anatomic diagnoses reported for ≥20% of subjects included single ventricle (52.0%) and hypoplastic left heart syndrome (29.5%). Fenestration was reported for 32.8% of subjects.

The profile of baseline abnormalities in medical and surgical history was similar between treatment groups (Table 9). Abnormalities are provided by subject in Listing 16.2.7.2.

Table 9: Abnormalities in Medical and Surgical Histories (Safety Population)

Subjects with:	Udenafil (N=200) n (%)	Placebo (N=200) n (%)	Total (N=400) n (%)
At least 1 abnormality in medical or surgical history	199 (99.5)	199 (99.5)	398 (99.5)
Fenestration	73 (36.5)	58 (29.0)	131 (32.8)
Pacemaker placed	16 (8.0)	11 (5.5)	27 (6.8)
Previous history of protein losing enteropathy	2 (1.0)	3 (1.5)	5 (1.3)
Previous history of plastic bronchitis	1 (0.5)	1 (0.5)	2 (0.5)
Liver biopsy	16 (8.0)	20 (10.0)	36 (9.0)
Latex allergy	4 (2.0)	6 (3.0)	10 (2.5)
Single ventricle anatomic diagnoses	199 (99.5)	199 (99.5)	398 (99.5)
A1: Single ventricle[a]	97 (48.5)	111 (55.5)	208 (52.0)
A2: Hypoplastic left heart syndrome[b]	64 (32.0)	54 (27.0)	118 (29.5)
A3: Other functional single ventricle not fitting any other categories[c]	38 (19.0)	32 (16.0)	70 (17.5)
A4: Unclassified[d]	0	2 (1.0)	2 (0.5)

a Includes double inlet left ventricle, double inlet right ventricle, mitral atresia, tricuspid atresia, unbalanced atrioventricular canal defect, heterotaxia syndrome, and other single ventricle (mostly left, mostly right, indeterminate).

b Includes aortic and mitral atresia, aortic atresia and mitral stenosis, aortic atresia and ventricular septal defect (well-developed mitral valve and left ventricle), aortic stenosis and mitral stenosis, aortic stenosis and mitral valve hypoplasia, hypoplastic aortic valve and mitral valve and left ventricle, and left ventricle, aortic stenosis and mitral atresia.

c Includes pulmonary atresia with intact ventricular septum, ventricular septal defect(s), tricuspid valve anomaly, D-loop double outlet right ventricle with 2 ventricles, double outlet left ventricle with two ventricles, D-loop transposition of the great arteries with 2 ventricles, L-loop transposition of the great arteries or L-loop double outlet right ventricle with 2 ventricles, mitral valve anomaly, hypoplastic left ventricle with ventricular septal defect(s), hypoplastic right ventricle with ventricular septal defect(s).

d Unable to classify diagnosis into A1, A2 or A3 categories.

Source: Table 14.1.7
Program: t_14_1_7.sas

Almost all subjects in each treatment group reported at least 1 prior medication (97.5% udenafil, 99.0% placebo). Common prior medications (≥20% of subjects in either treatment group) included acetylsalicylic acid (89.5% udenafil, 93.5% placebo), enalapril (27.5% udenafil, 31.0% placebo), and lisinopril (24.0% udenafil, 20.5% placebo).

The use of prior medications was similar between treatment groups (Table 10). Prior medications are provided by subject in Listing 16.2.8.3.

Table 10: Prior Medications Used by ≥5% of Subjects in Either Treatment Group (Safety Population)

ATC Class (Level 3)[a] Preferred Drug Name	Udenafil (N=200) n (%)	Placebo (N=200) n (%)
≥1 non-study medication	195 (97.5)	198 (99.0)
ACE inhibitors, plain	107 (53.5)	107 (53.5)
Enalapril	55 (27.5)	62 (31.0)
Lisinopril	48 (24.0)	41 (20.5)
Antithrombotic agents	189 (94.5)	193 (96.5)
Acetylsalicylic acid	179 (89.5)	187 (93.5)
Warfarin	14 (7.0)	7 (3.5)
Beta blocking agents	16 (8.0)	18 (9.0)
Carvedilol	4 (2.0)	11 (5.5)
Beta-lactam antibacterials, penicillins	12 (6.0)	13 (6.5)
Amoxicillin	9 (4.5)	10 (5.0)
Cardiac glycosides	17 (8.5)	11 (5.5)
Digoxin	17 (8.5)	11 (5.5)
High-ceiling diuretics	18 (9.0)	14 (7.0)
Furosemide	18 (9.0)	13 (6.5)
Hypnotics and sedatives	10 (5.0)	5 (2.5)
Melatonin	10 (5.0)	5 (2.5)
Multivitamins, combinations	24 (12.0)	26 (13.0)
Multivitamins	21 (10.5)	24 (12.0)
Potassium-sparing agents	12 (6.0)	14 (7.0)
Spironolactone	12 (6.0)	14 (7.0)
Vitamin A and D, incl. combinations of the two	14 (7.0)	13 (6.5)
Colecalciferol	13 (6.5)	12 (6.0)

ACE=angiotensin-converting enzyme; ATC=Anatomical-Therapeutic-Chemical; incl=including
a Subjects prescribed 2 or more drugs within an ATC class are counted only once at the class level. Therefore, the sum of preferred drug name frequencies can exceed the class frequency.
Source: Table 14.3.25
Program: T_14_3_25.sas

All but 1 subject in each treatment group reported at least 1 concomitant medication. Frequently reported concomitant medications (≥20% of subjects in either treatment group) included acetylsalicylic acid (92.5% udenafil, 96.0% placebo), enalapril (28.5% udenafil,

31.0% placebo), lisinopril (25.0% udenafil, 20.0% placebo), and paracetamol (20.5% udenafil, 14.0% placebo).

The use of concomitant medications was similar between treatment groups (Table 11). Concomitant medications are provided by subject in Listing 16.2.8.4.1 and Listing 16.2.8.4.2.

Table 11: Concomitant Medications Used by ≥5% of Subjects in Either Treatment Group (Safety Population)

ATC Class (Level 3)[a] Preferred Drug Name	Udenafil (N=200) n (%)	Placebo (N=200) n (%)
≥1 non-study medication	199 (99.5)	199 (99.5)
ACE inhibitors, plain	110 (55.0)	106 (53.0)
Enalapril	57 (28.5)	62 (31.0)
Lisinopril	50 (25.0)	40 (20.0)
Adrenergics for systemic use	16 (8.0)	12 (6.0)
Salbutamol	11 (5.5)	8 (4.0)
Angiotensin II antagonists, plain	11 (5.5)	5 (2.5)
Losartan	10 (5.0)	5 (2.5)
Antihistamines for system use	35 (17.5)	30 (15.0)
Loratadine	11 (5.5)	9 (4.5)
Antithrombotic agents	194 (97.0)	197 (98.5)
Acetylsalicylic acid	185 (92.5)	192 (96.0)
Warfarin	14 (7.0)	8 (4.0)
Beta blocking agents	17 (8.5)	23 (11.5)
Carvedilol	5 (2.5)	14 (7.0)
Beta-lactam antibacterials, penicillins	29 (14.5)	37 (18.5)
Amoxicillin	23 (11.5)	29 (14.5)
Cardiac glycosides	17 (8.5)	11 (5.5)
Digoxin	17 (8.5)	11 (5.5)
High-ceiling diuretics	18 (9.0)	14 (7.0)
Furosemide	18 (9.0)	13 (6.5)
Hypnotics and sedatives	17 (8.5)	11 (5.5)
Melatonin	13 (6.5)	7 (3.5)
Macrolides, lincosamides and streptogramins	12 (6.0)	10 (5.0)
Azithromycin	10 (5.0)	8 (4.0)
Multivitamins, combinations	26 (13.0)	29 (14.5)
Multivitamins	24 (12.0)	26 (13.0)
Other analgesics and antipyretics	50 (25.0)	35 (17.5)
Paracetamol	41 (20.5)	28 (14.0)
Potassium-sparing agents	13 (6.5)	16 (8.0)
Spironolactone	13 (6.5)	16 (8.0)
Topical products for joint and muscular pain	41 (20.5)	29 (14.5)
Ibuprofen	39 (19.5)	26 (13.0)
Vitamin A and D, incl. combinations of the two	16 (8.0)	18 (9.0)
Colecalciferol	15 (7.5)	17 (8.5)

ACE=angiotensin-converting enzyme; ATC=Anatomical-Therapeutic-Chemical; incl=including

a Subjects prescribed 2 or more drugs within an ATC class are counted only once at the class level. Therefore, the sum of preferred drug name frequencies can exceed the class frequency.

Source: Table 14.3.26
Program: T_14_3_26.sas

11.3 Measurements of Treatment Compliance

Mean percent compliance with study drug was 89.92% in the udenafil group and 89.97% in the placebo group (Table 14.3.1.1). Compliance results are listed by subject in Listing 16.2.5.1.

11.4 Efficacy Results and Tabulations of Individual Subject Data

11.4.1 Analysis of Efficacy

The primary aim of this study was to evaluate the effect of 26 weeks of treatment with udenafil on exercise capacity in adolescents with Fontan physiology, with a primary outcome of change in maximal VO_2 from baseline to Week 26. The udenafil group had a mean increase from baseline to Week 26 in maximal VO_2 compared to a mean decrease in the placebo group, and the primary analysis identified a statistical trend for the treatment difference (p=0.071). Importantly, all efficacy endpoints measured at VAT indicated greater exercise capacity in the udenafil group than the placebo group at Week 26 ($p \leq 0.05$).

After an initial summary of the protocol-specified primary endpoint (maximal VO_2), this summary of efficacy will focus on measures of exercise capacity at VAT. In addition, maximal VO_2 and VO_2 at VAT were summarized with units of mL/min in addition to the protocol-specified units of mL/kg/min. As each participant's VO_2 at Week 26 is compared to their baseline, the natural fluctuations in weight over 6 months would add variability and could be a source of bias for individual subjects and for the study population as a whole.

11.4.1.1 Overview of Results for VO_2 at VAT and Maximal VO_2

For the protocol-specified primary endpoint, the udenafil group had a mean increase from baseline to Week 26 in maximal VO_2 (44.40 mL/min) compared to a mean decrease in the placebo group (-3.65 mL/min). The least squares mean treatment group difference for change from baseline to Week 26 in maximal VO_2 was 41.04 mL/min (p=0.071). When standardized by each subject's body weight, the least squares mean treatment group difference was 0.64 mL/kg/min (p=0.092). Results were consistent across methods of imputation for missing data and analysis populations (Table 12).

For VO_2 at VAT, the udenafil group had a mean increase from baseline to Week 26 in VO_2 at VAT (29.65 mL/min) as compared to a mean decrease in the placebo group (-8.01 mL/min). The least squares mean treatment group difference for change from baseline to Week 26 in VO_2 at VAT was 41.58 mL/min (p=0.023). When standardized by each subject's body weight,

the least squares mean treatment group difference was 0.78 mL/kg/min (p=0.012). Results were consistent across methods of imputation for missing data and analysis populations (Table 12).

Table 12: Overview of Analyses of Change Between Week 26 and Baseline Visits for Maximal VO_2 and VO_2 at VAT

VO_2 Measure (units) Endpoint, Population, Imputation	Mean (Standard Deviation) Udenafil	Placebo	Difference LS Mean (SE)	p-value [a]
Maximal VO_2 (mL/kg/min)				
Change, ITT, LOCF	-0.23 (4.056)	-0.89 (3.672)	0.64 (0.377)	0.092
Maximal VO_2 (mL/min)				
Change, ITT, LOCF	44.40 (238.291)	-3.65 (222.417)	41.04 (22.709)	0.071
Change, ITT, OC	46.98 (244.914)	-3.84 (228.224)	44.68 (23.897)	0.062
Change, ITT, mean of non-missing[b]	60.68 (261.742)	-1.34 (235.417)	51.72 (24.090)	0.032
Change, PP, LOCF	42.23 (238.652)	6.17 (207.286)	31.40 (22.363)	0.161
LN (change), ITT, LOCF	0.03 (0.163)	-0.01 (0.195)	0.03 (0.018)	0.070
LN (change), ITT, OC	0.03 (0.168)	-0.01 (0.200)	0.04 (0.019)	0.061
LN (change), ITT, mean of non-missing[b]	0.04 (0.184)	-0.01 (0.202)	0.04 (0.019)	0.033
LN (change), PP, LOCF	0.03 (0.163)	0.00 (0.134)	0.02 (0.015)	0.176
VO_2 at VAT (mL/kg/min)				
Change, ITT, LOCF	-0.07 (2.998)	-0.68 (3.216)	0.78 (0.308)	0.012
VO_2 at VAT (mL/min)				
Change, ITT, LOCF	29.65 (177.023)	-8.01 (183.031)	41.58 (18.224)	0.023
Change, ITT, OC	32.52 (185.191)	-8.95 (193.508)	50.56 (20.074)	0.012
Change, ITT, mean of non-missing[b]	42.12 (185.414)	-10.81 (204.340)	58.31 (19.040)	0.002
Change, ITT, linear regression	37.66 (189.688)	-15.93 (204.787)	58.83 (19.403)	0.003
Change, PP, LOCF	27.95 (176.397)	-2.78 (175.846)	38.62 (17.945)	0.032
LN (change), ITT, LOCF	0.03 (0.168)	-0.02 (0.252)	0.05 (0.022)	0.024
LN (change), ITT, OC	0.03 (0.176)	-0.02 (0.267)	0.06 (0.025)	0.015
LN (change), ITT, mean of non-missing[b]	0.05 (0.180)	-0.02 (0.266)	0.07 (0.023)	0.005
LN (change), ITT, linear regression	0.04 (0.186)	-0.03 (0.268)	0.07 (0.023)	0.005
LN (change), PP, LOCF	0.03 (0.167)	0.00 (0.184)	0.04 (0.018)	0.028

ANCOVA=analysis of covariance; ITT=intent-to-treat; LOCF=last observation carried forward; LN=natural logarithm; LS=least squares; OC=observed cases; PP=per protocol; SE=standard error; VAT=ventilatory anaerobic threshold; VO_2=minute oxygen consumption

a P-value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline maximal VO_2.

b When the Week 26 value was missing, the mean of non-missing Week 26 values (ignoring treatment group) was imputed.

Source: Table 14.2.1.1.1, Table 14.2.1.1.2, Table 14.2.1.1.3, Table 14.2.1.1.4, Table 14.2.1.2.1, Table 14.2.1.2.2, Table 14.2.1.2.3, Table 14.2.1.2.4, Table 14.2.2.1.1, Table 14.2.3.1.1, Table 14.2.3.1.2, Table 14.2.3.1.3, Table 14.2.3.1.4, Table 14.2.3.1.5, Table 14.2.3.2.1, Table 14.2.3.2.2, Table 14.2.3.2.3, Table 14.2.3.2.4, Table 14.2.3.2.5, and Table 14.2.4.1.1

Program: T_14_2_1_1_1.sas, T_14_2_1_1_2.sas, T_14_2_1_1_3.sas, T_14_2_1_1_4.sas, T_14_2_1_2_1.sas, T_14_2_1_2_2.sas, T_14_2_1_2_3.sas, T_14_2_1_2_4.sas, T_14_2_2_1_1.sas,T_14_2_3_1_1.sas, T_14_2_3_1_2.sas, T_14_2_3_1_3.sas, t_14_2_3_1_4.sas, T_14_2_3_1_5.sas, T_14_2_3_2_1.sas, T_14_2_3_2_2.sas, T_14_2_3_2_3.sas, T_14_2_3_2_4.sas, T_14_2_3_2_5.sas, and T_14_2_4_1_1.sas

11.4.1.2 Protocol-specified Primary Efficacy Endpoint

The udenafil group had a mean increase from baseline to Week 26 in maximal VO_2 (44.40 mL/min) compared to a mean decrease in the placebo group (-3.65 mL/min). The least squares mean treatment group difference for change from baseline to Week 26 in maximal VO_2 was 41.04 mL/min (p=0.071). When standardized by each subject's body weight, the least squares mean treatment group difference was 0.64 mL/kg/min (p=0.092). The protocol-specified primary analysis of change from baseline to Week 26 in maximal VO_2 (expressed as mL/min and mL/kg/min) is summarized in Table 13.

Table 13: Protocol-specified Primary Efficacy Analysis: Change in Maximal VO_2 Between Week 26 and Baseline Visits Using Last Observation Carried Forward (ITT Population)

Endpoint (units) Statistic	Udenafil (N=200)	Placebo (N=200)	Difference LS Mean (SE)	p-value
Maximal VO_2 (mL/min)				
Baseline, mean (SD)	1562.00 (437.329)	1626.95 (413.992)	-64.54 (42.436)	0.129[a]
Week 26, mean (SD)	1606.40 (451.719)	1623.30 (432.153)	-16.50 (44.081)	0.708[a]
Change from baseline				
Mean (SD)	44.40 (238.291)	-3.65 (222.417)	41.04 (22.709)	0.071[b]
Median	30.00	0.00		
Interquartile range	-70.00, 170.00	-120.00, 120.00		
Minimum, maximum	-620.0, 950.0	-1170.0, 720.0		
Maximal VO_2 (mL/kg/min)				
Baseline, mean (SD)	27.84 (6.877)	28.01 (6.128)	-0.16 (0.652)	0.801[a]
Week 26, mean (SD)	27.61 (6.871)	27.12 (6.628)	0.50 (0.676)	0.463[a]
Change from baseline				
Mean (SD)	-0.23 (4.056)	-0.89 (3.672)	0.64 (0.377)	0.092[b]
Median	-0.17	-0.85		
Interquartile range	-2.55, 1.70	-3.13, 1.17		
Minimum, maximum	-12.0, 15.5	-16.5, 13.8		

ANCOVA=analysis of covariance; ANOVA=analysis of variance; ITT=intent-to-treat; LS=least squares; SD=standard deviation; SE=standard error; VO_2=minute oxygen consumption
a P-value was assessed using ANOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group.
b P-value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline maximal VO_2.
Source: Table 14.2.1.1.1 and Table 14.2.2.1.1
Program: T_14_2_1_1_1.sas and T_14_2_2_1_1.sas

Results for treatment group differences in change from baseline in maximal VO_2 using units of mL/min were generally similar for analyses using no imputation (p=0.062, Table 14.2.1.1.2), imputation with the mean of non-missing values at Week 26 (p=0.032, Table 14.2.1.1.3), and last observation carried forward (LOCF) for Per Protocol population (p=0.161, Table 14.2.1.1.4). Analysis of ranked changes using LOCF (Table 14.2.1.1.5) and imputation with zero (Table 14.2.1.1.6) demonstrated $p<0.05$ for treatment differences (p=0.026 and p=0.045, respectively).

Results for treatment group differences in change from baseline in maximal VO_2 using units of mL/kg/min were generally similar for analyses using no imputation (p=0.089, Table 14.2.2.1.2), imputation with the mean of non-missing values at Week 26 (p=0.083, Table 14.2.2.1.3), LOCF for Per Protocol population (p=0.188, Table 14.2.2.1.4), ranked changes (p=0.069, Table 14.2.2.1.5), and imputation with zero (p=0.422, Table 14.2.2.1.6).

Waterfall plots for change in maximal VO_2 from baseline to Week 26 are presented in Figure 14.2.1.1.3 for units of mL/min and in Figure 14.2.1.1.4 for units of mL/kg/min. The cumulative distribution curve for change in maximal VO_2 from baseline to Week 26 is presented in Figure 14.2.1.1.5 for units of mL/kg/min. For these figures, no imputation was performed for missing observations.

The udenafil group had a mean increase from baseline to Week 26 in the natural logarithm of maximal VO_2 (0.03) compared to a mean decrease in the placebo group (-0.01). The least squares mean treatment group difference for change from baseline to Week 26 in the natural logarithm of maximal VO_2 was 0.03 (p=0.070). Change from baseline to Week 26 in maximal VO_2 (displayed as natural logarithms of mL/min and mL/kg/min) is summarized in Table 14.

Table 14: Change in the Natural Logarithm of Maximal VO_2 Between Week 26 and Baseline Visits Using Last Observation Carried Forward (ITT Population)

Endpoint (units) Statistic	Udenafil (N=200)	Placebo (N=200)	Difference LS Mean (SE)	p-value
Maximal VO_2 (natural logarithm of mL/min)				
Baseline, mean (SD)	7.32 (0.280)	7.36 (0.251)	-0.05 (0.027)	0.075[a]
Week 26, mean (SD)	7.34 (0.276)	7.35 (0.301)	-0.01 (0.029)	0.765[a]
Change from baseline				
Mean (SD)	0.03 (0.163)	-0.01 (0.195)	0.03 (0.018)	0.070[b]
Median	0.02	0.00		
Interquartile range	-0.04, 0.10	-0.09, 0.07		
Minimum, maximum	-0.5, 1.0	-2.0, 0.4		
Maximal VO_2 (natural logarithm of mL/kg/min)				
Baseline, mean (SD)	3.30 (0.250)	3.31 (0.221)	-0.01 (0.024)	0.603[a]
Week 26, mean (SD)	3.29 (0.257)	3.27 (0.287)	0.02 (0.027)	0.446[a]
Change from baseline				
Mean (SD)	-0.01 (0.163)	-0.04 (0.191)	0.03 (0.018)	0.072[b]
Median	-0.01	-0.03		
Interquartile range	-0.10, 0.07	-0.13, 0.04		
Minimum, maximum	-0.05, 1.0	-2.0, 0.4		

ANCOVA=analysis of covariance; ANOVA=analysis of variance; ITT=intent-to-treat; LS=least squares; SD=standard deviation; SE=standard error; VO_2=minute oxygen consumption
a P-value was assessed using ANOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group.
b P-value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline maximal VO_2.
Note: Values are summarized as natural logarithm of maximal VO_2.
Source: Table 14.2.1.2.1 and Table 14.2.2.2.1
Program: T_14_2_1_2_1.sas and T_14_2_2_2_1.sas

Results for treatment group differences in change of the natural logarithm for maximal VO_2 using units of mL/min were generally similar for analyses using no imputation (p=0.061, Table 14.2.1.2.2), imputation with the mean of non-missing values at Week 26 (p=0.033, Table 14.2.1.2.3), and LOCF for Per Protocol population (p=0.176, Table 14.2.1.2.4).

Results for treatment group differences in change of the natural logarithm for maximal VO_2 using units of mL/kg/min were generally similar for analyses using no imputation (p=0.073, Table 14.2.2.2.2), imputation with the mean of non-missing values at Week 26 (p=0.075, Table 14.2.2.2.3), and LOCF for Per Protocol population (p=0.202, Table 14.2.2.2.4).

Exercise results are presented by subject in Listing 16.2.6.1.1, Listing 16.2.6.1.2, Listing 16.2.6.1.3, Listing 16.2.6.1.4, Listing 16.2.6.1.5, and Listing 16.2.6.1.5.1.

11.4.1.3 VO_2 at Ventilatory Anaerobic Threshold

The udenafil group had a mean increase from baseline to Week 26 in VO_2 at VAT (29.65 mL/min) as compared to a mean decrease in the placebo group (-8.01 mL/min). The least squares mean treatment group difference for change from baseline to Week 26 in VO_2 at VAT was 41.58 mL/min (p=0.023). When standardized by each subject's body weight, the least squares mean treatment group difference was 0.78 mL/kg/min (p=0.012). The analysis of change from baseline to Week 26 in VO_2 at VAT (expressed as mL/min and mL/kg/min) is summarized in Table 15.

Table 15: Change in VO_2 at VAT Between Week 26 and Baseline Visits Using Last Observation Carried Forward (ITT Population)

	Udenafil (N=200)	Placebo (N=200)	Difference LS Mean (SE)	p-value
VO_2 at VAT (mL/min)				
Baseline	n=170	n=181		
Mean (SD)	1039.41 (300.779)	1020.50 (279.683)	19.06 (30.963)	0.539[a]
Week 26	n=185	n=191		
Mean (SD)	1059.03 (291.999)	1014.45 (277.017)	56.72 (30.595)	0.065[a]
Difference, Week 26 minus baseline	n=170	n=181		
Mean (SD)	29.65 (177.023)	-8.01 (183.031)	41.58 (18.224)	0.023[b]
Median	20.00	0.00		
VO_2 at VAT (mL/kg/min)				
Baseline	n=170	n=181		
Mean (SD)	18.35 (4.633)	17.71 (4.304)	0.64 (0.478)	0.181[a]
Week 26	n=185	n=191		
Mean (SD)	18.20 (4.509)	16.99 (4.130)	1.25 (0.465)	0.008[a]
Difference, Week 26 minus baseline	n=170	n=181		
Mean (SD)	-0.07 (2.998)	-0.68 (3.216)	0.78 (0.308)	0.012[b]
Median	0.00	-0.25		

ANCOVA=analysis of covariance; ANOVA=analysis of variance; ITT=intent-to-treat; LS=least squares; SD=standard deviation; SE=standard error; VAT=ventilatory anaerobic threshold; VO_2=minute oxygen consumption
a P-value was assessed using ANOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group.
b P-value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline maximal VO_2.
Source: Table 14.2.3.1.1 and Table 14.2.4.1.1
Program: T_14_2_3_1_1.sas and T_14_2_4_1_1.sas

Results for treatment group differences in change from baseline in VO_2 at VAT using units of mL/min were generally similar for analyses using no imputation (p=0.012, Table 14.2.3.1.2), imputation with the mean of non-missing values at Week 26 (p=0.002, Table 14.2.3.1.3), imputation using linear regression (p=0.003, Table 14.2.3.1.4), LOCF for Per Protocol population (p=0.032, Table 14.2.3.1.5), and ranked changes (p=0.075, Table 14.2.3.1.6).

Results for treatment group differences in change from baseline in VO_2 at VAT using units of mL/kg/min were generally similar for analyses using no imputation (p=0.009,

Table 14.2.4.1.2), imputation with the mean of non-missing values at Week 26 (p=0.007, Table 14.2.4.1.3), imputation using linear regression (p=0.003, Table 14.2.4.1.4), LOCF for Per Protocol population (p=0.019, Table 14.2.4.1.5), and ranked changes (p=0.152, Table 14.2.4.1.6).

Waterfall plots for change in VO_2 at VAT from baseline to Week 26 are presented in Figure 14.2.2.1.3 for units of mL/min and in Figure 14.2.2.1.4 for units of mL/kg/min. The cumulative distribution curve for change in VO_2 at VAT from baseline to Week 26 is presented in Figure 14.2.2.1.5 for units of mL/kg/min. For these figures, no imputation was performed for missing observations.

When change in the natural logarithm of VO_2 at VAT was based on units of mL/min, the udenafil group had a mean increase from baseline to Week 26 in VO_2 at VAT (0.03) compared to a mean decrease in the placebo group (-0.02). The least squares mean treatment group difference for change from baseline to Week 26 in the natural logarithm of VO_2 at VAT was 0.05 (p=0.024). Change from baseline to Week 26 in VO_2 at VAT (displayed as natural logarithms of mL/min and mL/kg/min) is summarized in Table 16.

Table 16: Change in the Natural Logarithm of VO_2 at VAT Between Week 26 and Baseline Visits Using Last Observation Carried Forward (ITT Population)

	Udenafil (N=200)	Placebo (N=200)	Difference LS Mean (SE)	p-value
VO_2 at VAT (natural logarithm of mL/min)				
Baseline	n=170	n=181		
Mean (SD)	6.91 (0.280)	6.89 (0.262)	0.01 (0.029)	0.629[a]
Week 26	n=185	n=191		
Mean (SD)	6.93 (0.267)	6.88 (0.322)	0.06 (0.032)	0.054[a]
Difference, Week 26 minus baseline	n=170	n=181		
Mean (SD)	0.03 (0.168)	-0.02 (0.252)	0.05 (0.022)	0.024[b]
Median	0.02	0.00		
VO_2 at VAT (natural logarithm of mL/kg/min)				
Baseline	n=170	n=181		
Mean (SD)	2.88 (0.249)	2.85 (0.241)	0.03 (0.026)	0.203[a]
Week 26	n=185	n=191		
Mean (SD)	2.87 (0.249)	2.80 (0.308)	0.08 (0.030)	0.013[a]
Difference, Week 26 minus baseline	n=170	n=181		
Mean (SD)	0.00 (0.170)	-0.05 (0.253)	0.05 (0.023)	0.029[b]
Median	0.00	-0.02		

ANCOVA=analysis of covariance; ANOVA=analysis of variance; ITT=intent-to-treat; LS=least squares; SD=standard deviation; SE=standard error; VAT=ventilatory anaerobic threshold; VO_2=minute oxygen consumption
a P-value was assessed using ANOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group.
b P-value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline maximal VO_2.
Note: Values are summarized as natural logarithm of maximal VO_2 at VAT.
Source: Table 14.2.3.2.1 and Table 14.2.4.2.1
Program: T_14_2_3_2_1.sas and T_14_2_4_2_1.sas

Results for treatment group differences in change of the natural logarithm for VO_2 at VAT from baseline using units of mL/min were generally similar for analyses using no imputation (p=0.015, Table 14.2.3.2.2), imputation with the mean of non-missing values at Week 26 (p=0.005, Table 14.2.3.2.3), imputation with linear regression (p=0.005, Table 14.2.3.2.4), and LOCF for Per Protocol population (p=0.028, Table 14.2.3.2.5).

Results for treatment group differences in change of the natural logarithm for VO_2 at VAT from baseline using units of mL/kg/min were generally similar for analyses using no imputation (p=0.026, Table 14.2.4.2.2), imputation with the mean of non-missing values at

Week 26 (p=0.024, Table 14.2.4.2.3), imputation using linear regression (p=0.013, Table 14.2.4.2.4), and LOCF for Per Protocol population (p=0.038, Table 14.2.4.2.5).

11.4.1.4 Secondary Efficacy Endpoints

11.4.1.4.1 Secondary Efficacy Endpoints Measured at Ventilatory Anaerobic Threshold

The 2 secondary efficacy endpoints measured at VAT indicated greater exercise capacity in the udenafil group than the placebo group at Week 26:

- VE/VCO_2 at VAT: Greater mean decrease (improvement) for udenafil (-0.76) as compared to placebo (-0.05) at Week 26 (p=0.011)
- Work rate at VAT: Greater mean increase (improvement) for udenafil (3.46 watts) as compared to placebo (0.31 watts) at Week 26 (p=0.029)

Change in secondary exercise endpoints measured at VAT from baseline to Week 26 are summarized in Table 17.

Table 17: Difference in Secondary Exercise Endpoints Measured at Ventilatory Anaerobic Threshold Between Week 26 and Baseline Visits Using Last Observation Carried Forward (ITT Population)

Exercise Endpoint	Udenafil (N=200)	Placebo (N=200)	Difference LS Mean (SE)	p-value
VE/VCO_2 at VAT				
Baseline	n=170	n=181		
Mean (SD)	34.32 (4.845)	34.75 (5.157)	-0.42 (0.536)	0.431[a]
Week 26	n=185	n=191		
Mean (SD)	33.60 (4.833)	34.67 (4.872)	-1.13 (0.509)	0.027[a]
Difference, Week 26 – baseline	n=170	n=181		
Mean (SD)	-0.76 (3.564)	-0.05 (2.967)	-0.82 (0.321)	0.011[b]
Median	0.00	0.00		
Work rate at VAT (watts)				
Baseline	n=167	n=177		
Mean (SD)	66.19 (26.321)	66.10 (23.446)	0.12 (2.688)	0.963[a]
Week 26	n=181	n=186		
Mean (SD)	69.20 (26.171)	66.62 (22.710)	3.30 (2.660)	0.215[a]
Difference, Week 26 – baseline	n=167	n=177		
Mean (SD)	3.46 (15.076)	0.31 (13.246)	3.20 (1.460)	0.029[b]
Median	1.00	0.00		

ANCOVA=analysis of covariance; ANOVA=analysis of variance; ITT=intent-to-treat; LS=least squares; SD=standard deviation; SE=standard error; VAT=ventilatory anaerobic threshold; VE/VCO_2=ventilatory equivalents of carbon dioxide; VO_2=minute oxygen consumption

a P-value was assessed using ANOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group.

b P-value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline maximal VO_2.

Source: Table 14.2.13.1.1 and Table 14.2.14.1.1
Program: T_14_2_13_1_1.sas and T_14_2_14_1_1.sas

Results for treatment group differences in change from baseline for VE/VCO_2 at VAT were generally similar for analyses using no imputation (p=0.014, Table 14.2.13.1.2) and imputation with the mean of non-missing values at Week 26 (p=0.044, Table 14.2.13.1.3). Results for treatment group differences in percent change from baseline for VE/VCO_2 at VAT were generally similar for analyses using LOCF (p=0.008, Table 14.2.13.2.1), no imputation (p=0.010, Table 14.2.13.2.2), and imputation with the mean of non-missing values at Week 26 (p=0.035, Table 14.2.13.2.3).

Results for treatment group differences in change from baseline for work rate at VAT were generally similar for analyses using no imputation (p=0.021, Table 14.2.14.1.2) and imputation with the mean of non-missing values at Week 26 (p=0.011, Table 14.2.14.1.3). Results for treatment group differences in percent change from baseline for work rate at VAT

were generally similar for analyses using LOCF (p=0.053, Table 14.2.14.2.1), no imputation (p=0.035, Table 14.2.14.2.2), and imputation with the mean of non-missing values at Week 26 (p=0.030, Table 14.2.14.2.3).

11.4.1.4.2 Secondary Efficacy Endpoints Measured at Peak Exercise

The treatment group difference for change from baseline to Week 26 in VE/VCO_2 at peak exercise was statistically significant (p=0.005). A mean decrease of -1.24 was observed in the udenafil group as compared to a mean increase of 0.04 in the placebo group. For other efficacy endpoints measured at peak exercise (minute VO_2, respiratory rate, minute ventilation, work rate, heart rate, and RER), treatment group differences for change from baseline to Week 26 did not achieve $p \leq 0.05$. The change in secondary efficacy endpoints measured at peak exercise from baseline to Week 26 is summarized in Table 18.

Table 18: Change in Secondary Efficacy Endpoints Measured at Peak Exercise Between Week 26 and Baseline Visits Using Last Observation Carried Forward (ITT Population)

Exercise Endpoint	Udenafil (N=200)	Placebo (N=200)	Difference LS Mean (SE)	p-value[a]
Minute VO_2 (L/minute)	n=200	n=200		
Difference, Week 26 – baseline, mean (SD)	0.04 (0.238)	0.00 (0.222)	0.04 (0.023)	0.071
Respiratory rate (breaths/minute)	n=199	n=200		
Difference, Week 26 – baseline, mean (SD)	-1.01 (10.030)	-1.44 (9.928)	0.35 (0.903)	0.696
Minute ventilation (L/minute)	n=199	n=200		
Difference, Week 26 – baseline, mean (SD)	1.15 (13.934)	-0.10 (13.748)	0.14 (1.319)	0.915
Work rate (watts)	n=198	n=199		
Difference, Week 26 – baseline, mean (SD)	2.99 (14.334)	2.45 (13.503)	0.19 (1.363)	0.891
Heart rate (beats/minute)	n=200	n=200		
Difference, Week 26 – baseline, mean (SD)	-1.36 (10.773)	-2.41 (12.714)	0.66 (1.140)	0.563
Respiratory exchange ratio	n=200	n=200		
Difference, Week 26 – baseline, mean (SD)	0.02 (0.117)	0.01 (0.073)	0.01 (0.008)	0.275
VE/VCO_2	n=199	n=200		
Difference, Week 26 – baseline, mean (SD)	-1.24 (5.181)	0.04 (6.092)	-1.46 (0.519)	0.005

ANCOVA=analysis of covariance; ITT=intent-to-treat; LS=least squares; SD=standard deviation; SE=standard error; VE/VCO_2=ventilatory equivalents of carbon dioxide; VO_2=minute oxygen consumption

a P-value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline maximal VO_2.

Source: Table 14.2.5.1.1, Table 14.2.7.1.1, Table 14.2.8.1.1, Table 14.2.9.1.1, Table 14.2.10.1.1, Table 14.2.11.1.1, and Table 14.2.12.1.1

Program: T_14_2_5_1_1.sas, T_14_2_7_1_1.sas, T_14_2_8_1_1.sas, T_14_2_9_1_1.sas, T_14_2_10_1_1.sas, T_14_2_11_1_1.sas, and T_14_2_12_1_1.sas

Results based on LOCF, no imputation (observed cases), and imputation with the mean of non-missing values at Week 26 are presented for each measure at peak exercise as shown below.

Measure at Peak Exercise	LOCF		Observed Cases		Week 26 Mean	
	Change	% Change	Change	% Change	Change	% Change
Minute VO_2	14.2.5.1.1	14.2.5.2.1	14.2.5.1.2	14.2.5.2.2	14.2.5.1.3	14.2.5.2.3
Respiratory rate	14.2.7.1.1	14.2.7.2.1	14.2.7.1.2	14.2.7.2.2	14.2.7.1.3	14.2.7.2.3
Minute ventilation	14.2.8.1.1	14.2.8.2.1	14.2.8.1.2	14.2.8.2.2	14.2.8.1.3	14.2.8.2.3
Work rate	14.2.9.1.1	14.2.9.2.1	14.2.9.1.2	14.2.9.2.2	14.2.9.1.3	14.2.9.2.3
Heart rate	14.2.10.1.1	14.2.10.2.1	14.2.10.1.2	14.2.10.2.2	14.2.10.1.3	14.2.10.2.3
Respiratory exchange ratio	14.2.11.1.1	14.2.11.2.1	14.2.11.1.2	14.2.11.2.2	14.2.11.1.3	14.2.11.2.3
VE/VCO_2	14.2.12.1.1	14.2.12.2.1	14.2.12.1.2	14.2.12.2.2	14.2.12.1.3	14.2.12.2.3

LOCF=last observation carried forward; VE/VCO_2=ventilatory equivalents of carbon dioxide; VO_2=minute oxygen consumption

11.4.1.4.3 Other Secondary Efficacy Endpoints

A decrease in MPI (improvement in function) from baseline to Week 26 was observed in the udenafil group (-0.02) as compared to an increase in the placebo group (0.01). The least squares mean treatment difference for change in MPI from baseline to Week 26 was -0.03 (p=0.024). Change in MPI from baseline to Week 26 is summarized in Table 19.

Treatment group differences for the remaining ECHO endpoints did not achieve $p \leq 0.05$ (Table 14.2.15.1, Table 14.2.15.2, Table 14.2.15.3, Table 14.2.15.4, Table 14.2.15.5, Table 14.2.15.6, Table 14.2.15.7, Table 14.2.15.8, Table 14.2.15.9, Table 14.2.15.10, and Table 14.2.15.11). Results for individual subjects are presented in Listing 16.2.6.2.1, Listing 16.2.6.2.2.1, and Listing 16.2.6.2.2.2.

Table 19: Change in Myocardial Performance Index Between Week 26 and Baseline Visits (ITT Population)

	Udenafil (N=200)	Placebo (N=200)	Difference LS Mean (SE)	p-value
Baseline	n=150	n=155		
Mean (SD)	0.45 (0.172)	0.45 (0.154)	-0.00 (0.018)	0.925[a]
Week 26	n=146	n=147		
Mean (SD)	0.42 (0.147)	0.46 (0.177)	-0.04 (0.019)	0.022[a]
Difference, Week 26 – baseline	n=122	n=127		
Mean (SD)	-0.02 (0.112)	0.01 (0.132)	-0.03 (0.014)	0.024[b]
Median	-0.01	0.01		

ANCOVA=analysis of covariance; ANOVA=analysis of variance; ITT=intent-to-treat; LS=least squares; SD=standard deviation; SE=standard error
a P-value was assessed using ANOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group.
b P-value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline maximal minute oxygen consumption.
Note: No imputation was performed.
Source: Table 14.2.15
Program: T_14_2_15.sas

The increase in log-transformed reactive hyperemia index from baseline to Week 26 was larger in the udenafil group (0.06) than in the placebo group (0.04). The least squares mean treatment difference for change in log-transformed reactive hyperemia index from baseline to Week 26 was 0.02 (p=0.410).

The increase in log-transformed BNP from baseline to Week 26 was larger in the udenafil group (0.08 pg/mL) than in the placebo group (0.03 pg/mL). The least squares mean treatment difference for change in log-transformed BNP from baseline to Week 26 was 0.13 pg/mL (p=0.169).

The change in log-transformed reactive hyperemia index and BNP from baseline to Week 26 is summarized in Table 20. Results for individual subjects are presented in Listing 16.2.6.2.3 for BNP and in Listing 16.2.6.2.4 for log-transformed reactive hyperemia index.

Table 20: Change in Endothelial Function and Brain Natriuretic Peptide Between Week 26 and Baseline Visits (ITT Population)

Endpoint	Udenafil (N=200)	Placebo (N=200)	Difference LS Mean (SE)	p-value[a]
Log-transformed reactive hyperemia index	n=175	n=184		
Difference, Week 26 – baseline, mean (SD)	0.06 (0.301)	0.04 (0.364)	0.02 (0.029)	0.410
Log-transformed brain natriuretic peptide (pg/mL)	n=187	n=191		
Difference, Week 26 – baseline, mean (SD)	0.08 (0.905)	0.03 (1.137)	0.13 (0.094)	0.169

ANCOVA=analysis of covariance; ITT=intent-to-treat; LS=least squares; SD=standard deviation; SE=standard error
a P-value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline maximal minute oxygen consumption.
Note: Brain natriuretic peptide values reported by the laboratory as <2.0 were imputed as 1.0.
Source: Table 14.2.16 and Table 14.2.17
Program: T_14_2_16.sas and T_14_2_17.sas

Change in PedsQL child-reported and parent-reported scale scores from baseline to Week 26 were generally small; no treatment group difference achieved $p \leq 0.05$ (Table 21). Results for individual subjects are presented in Listing 16.2.6.3.1, Listing 16.2.6.3.2, Listing 16.2.6.3.3, and Listing 16.2.6.3.4.

Table 21: Difference in Pediatric Quality of Life Inventory Endpoints Between Week 26 and Baseline Visits (ITT Population)

	Udenafil (N=200)	Placebo (N=200)	LS Mean Difference (SE)	p-value[a]
PedsQL Generic Core Scales				
Physical functioning (child-reported)	n=186	n=193		
Difference, Week 26 – baseline, mean (SD)	2.08 (12.006)	1.53 (11.823)	0.44 (1.100)	0.691
Physical functioning (parent-reported)	n=181	n=181		
Difference, Week 26 – baseline, mean (SD)	2.74 (18.011)	1.94 (15.328)	0.03 (1.544)	0.985
Psychosocial health summary score (child-reported)	n=185	n=193		
Difference, Week 26 – baseline, mean (SD)	2.84 (11.356)	1.74 (10.700)	1.14 (1.039)	0.273
Psychosocial health summary score (parent-reported)	n=181	n=181		
Difference, Week 26 – baseline, mean (SD)	2.64 (13.546)	2.15 (13.737)	-0.06 (1.327)	0.966
PedsQL Cardiac Module Scales				
Treatment II (child-reported)	n=164	n=173		
Difference, Week 26 – baseline, mean (SD)	0.24 (11.655)	-0.09 (9.046)	-0.38 (1.011)	0.706
Perceived physical appearance	n=184	n=192		
Difference, Week 26 – baseline, mean (SD)	2.45 (20.819)	0.78 (17.396)	1.50 (1.707)	0.382
Treatment anxiety	n=184	n=192		
Difference, Week 26 – baseline, mean (SD)	3.37 (19.258)	1.66 (16.477)	1.91 (1.611)	0.236
Cognitive problems	n=183	n=192		
Difference, Week 26 – baseline, mean (SD)	2.19 (16.826)	3.05 (17.027)	-0.99 (1.622)	0.543
Communication problems	n=183	n=192		
Difference, Week 26 – baseline, mean (SD)	1.82 (20.406)	4.36 (17.954)	-1.66 (1.780)	0.352

ANCOVA=analysis of covariance; ITT=intent-to-treat; LS=least squares; PedsQL=Pediatric Quality of Life Inventory; SD=standard deviation; SE=standard error
a P-value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline value.
Source: Table 14.2.18.1, Table 14.2.18.2, Table 14.2.18.3, Table 14.2.18.4, Table 14.2.18.5, Table 14.2.18.6, Table 14.2.18.7, Table 14.2.18.8, and Table 14.2.18.9
Program: 14_2_18.sas

Mean treatment group differences in change from baseline to Week 26 in PCQLI child-reported and parent-reported total scores were generally small; no treatment group

difference achieved p≤0.05 (Table 22). Results for individual subjects are presented in Listing 16.2.6.4.1 and Listing 16.2.6.4.2.

Table 22: Difference in Pediatric Cardiac Quality of Life Inventory Endpoints Between Week 26 and Baseline Visits (ITT Population)

PCQLI Score	Udenafil (N=200)	Placebo (N=200)	LS Mean Difference (SE)	p-value[a]
Total score for 8-12 (child-reported)	n=16	n=12		
Difference, Week 26 – baseline, mean (SD)	3.26 (12.287)	-2.37 (16.368)	3.59 (5.684)	0.533
Total score for 8-12 (parent-reported)	n=17	n=11		
Difference, Week 26 – baseline, mean (SD)	-0.91 (13.399)	-4.44 (6.389)	1.84 (4.057)	0.654
Total score for 13-18 (child-reported)	n=158	n=170		
Difference, Week 26 – baseline, mean (SD)	-0.08 (11.032)	0.09 (9.626)	-0.05 (1.069)	0.963
Total score for 13-18 (parent-reported)	n=152	n=162		
Difference, Week 26 – baseline, mean (SD)	0.36 (11.722)	-1.60 (11.179)	1.36 (1.171)	0.246

ANCOVA=analysis of covariance; ITT=intent-to-treat; LS=least squares; PCQLI=Pediatric Cardiac Quality of Life Inventory; SD=standard deviation; SE=standard error
a P-value was assessed using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group with a continuous covariate of baseline value.
Source: Table 14.2.19.1, Table 14.2.19.2, Table 14.2.19.3, and Table 14.2.19.4
Program: 14_2_19.sas

11.4.2 Statistical/Analytical Issues

11.4.2.1 Adjustments for Covariates

The primary efficacy endpoint (aerobic exercise performance) and some of the secondary efficacy endpoints were analyzed with an ANCOVA model with fixed factors for ventricular morphology and treatment groups with a covariate of the relevant baseline value.

11.4.2.2 Handling of Dropouts or Missing Data

The following imputation method was used for the primary analysis of the primary outcome:

- Subjects who died or dropped out of the study with unknown vital status were to be assigned a maximal VO_2 of zero at Week 26. No subject met this criterion.
- Subjects who were known to be alive, but who discontinued from the study (and were missing maximal VO_2 at Week 26) were assigned the latest value available.

- Subjects who completed Week 26 but were physically unable to reach maximum effort in cardiopulmonary exercise testing after 2 attempts, were assigned their baseline value (ie, zero change).

Two additional sensitivity analyses to assess the impact of missing data were conducted as follows:

- Subjects with missing maximal VO_2 at Week 26 were assigned a maximal VO_2 of zero.

- Subjects with missing maximal VO_2 at Week 26 were excluded from analysis (ie, observed cases analysis).

An additional imputation method for missing data was included for exercise variables. When the Week 26 value was missing, the mean of non-missing Week 26 values (ignoring treatment group) was imputed.

For VO_2 at VAT, a linear regression model was used to predict Week 26 VO_2 at VAT from Week 26 maximal VO_2. The predicted value from the model was used to impute VO_2 at VAT when maximal VO_2 was available; when maximal VO_2 was also missing, the average from all subjects with non-missing values was imputed.

Missing item scores for rating scales were imputed according to published methodology for the scale. Otherwise, missing data were not estimated for secondary efficacy endpoints.

11.4.2.3 Interim Analyses and Data Monitoring

The PHN DSMB convened at least twice per year to review safety data. In addition, the DSMB was asked to review all data after the first 50 subjects had completed the study.

Formal stopping boundaries were not proposed for the 26-week study. However, the DSMB could have recommended stopping the study for other reasons, such as safety findings from this study and other studies or concerns about study conduct. In addition, premature termination of this study could have occurred due to the impact of results released from other studies, due to failure to enroll, or due to withdrawal of study approval by clinical site IRBs. In addition, the NHLBI retained the right to discontinue the study prior to the inclusion of the intended number of subjects but intended to exercise these rights only for valid scientific or administrative reasons.

After primary outcome data were obtained for approximately half of the originally planned sample size (approximately N=200 subjects), the variance of the primary outcome was estimated using a blinded method with lumped variance. If this estimated variance was higher than the one used for the sample size calculations, then the sample size would have been recalculated and increased correspondingly. Otherwise, the sample size would not change, and the study would proceed as planned. This approach was based on blinded re-estimation of nuisance parameters and did not lead to inflation of type I error. It was consistent with the regulatory guidance for industry in adaptive design of clinical studies.

The estimated variance at the interim analysis did not require an increase in sample size.

11.4.2.4 Multicenter Studies

The study was conducted at 30 sites. Change in maximal VO_2 is summarized by site in Table 14.2.1.2.5 using units of mL/min and in Table 14.2.2.2.5 using units of mL/kg/min. Change in VO_2 at VAT is summarized by site in Table 14.2.3.2.6 using units of mL/min and in Table 14.2.4.2.6 using units of mL/kg/min.

11.4.2.5 Multiple Comparison/Multiplicity

Formal hypothesis testing was performed only for the primary efficacy endpoint. No adjustment for multiple comparisons was made for secondary efficacy endpoints.

11.4.2.6 Use of an "Efficacy Subset" of Subjects

The primary efficacy analysis was performed with the ITT population, which included all randomized subjects and was the primary population for efficacy analyses. Sensitivity analyses were performed for the Per Protocol population (Table 14.2.1.1.4, Table 14.2.1.2.4, Table 14.2.2.1.4, and Table 14.2.2.2.4), which included all treated subjects who met all entry criteria or, if criteria were not met, were granted a waiver by the Sponsor; subjects with major protocol deviations were excluded.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

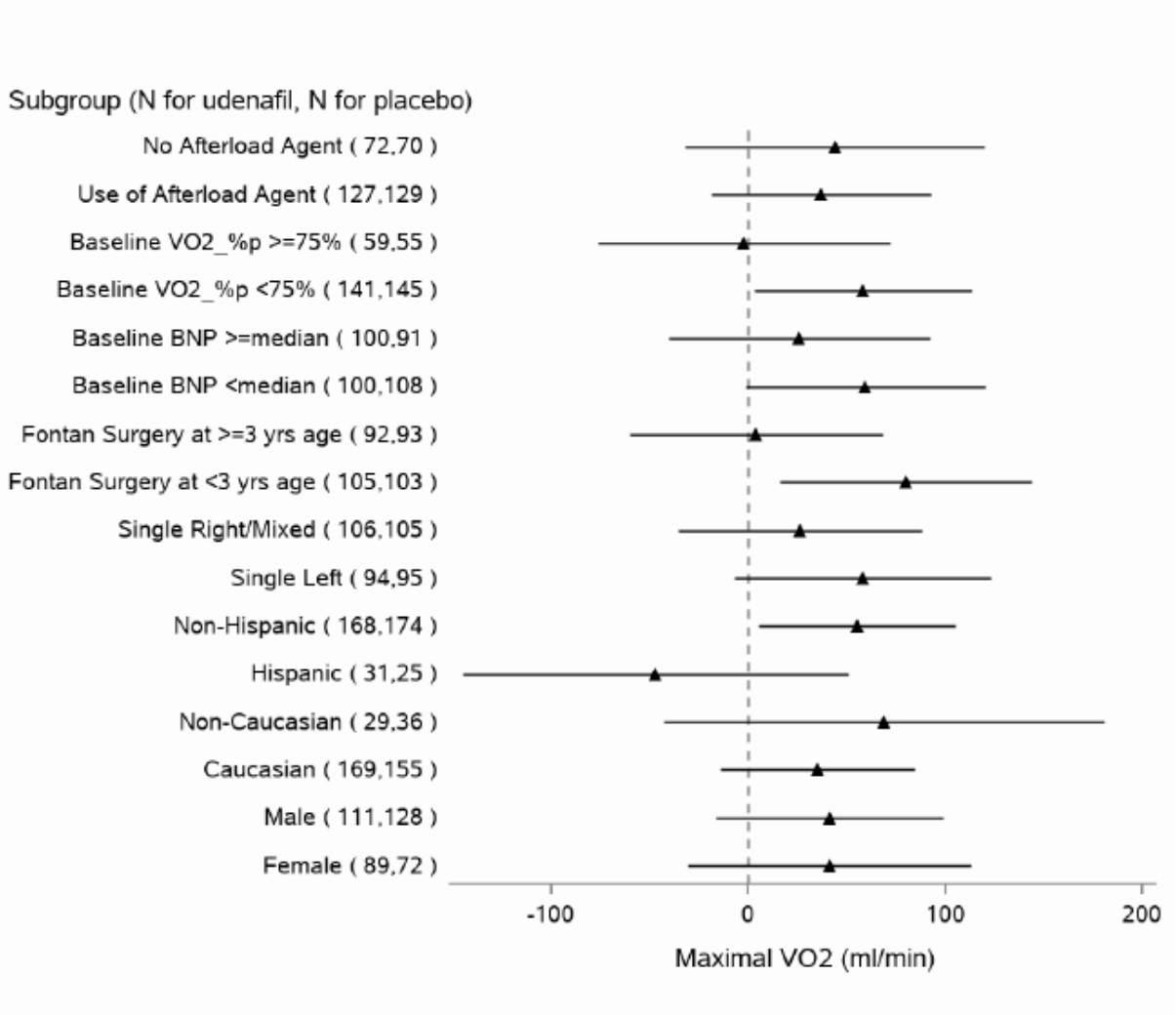
An active control was not used in this study.

11.4.2.8 Examination of Subgroups

The treatment group difference (udenafil minus placebo) for change in maximal VO_2 from baseline to Week 26 was positive for most subgroups (Figure 2). Positive differences indicate greater mean improvement from baseline for udenafil than for placebo.

Treatment group differences are also presented in mL/min without imputation by gender (Table 14.2.1.1.2.1), race (Table 14.2.1.1.2.2), ethnicity (Table 14.2.1.1.2.3), ventricular morphology (Table 14.2.1.1.2.4), age at Fontan surgery (Table 14.2.1.1.2.5), baseline serum BNP (Table 14.2.1.1.2.6), percent predicted maximal VO_2 at baseline (Table 14.2.1.1.2.7), and use of afterload reducing agents (Table 14.2.1.1.2.8).

Figure 2: **Treatment Group Difference in Mean Maximal VO_2 (mL/min) With 95% Confidence Interval for Change Between Week 26 and Baseline Visits in Subpopulations Using Last Observation Carried Forward (ITT Population)**



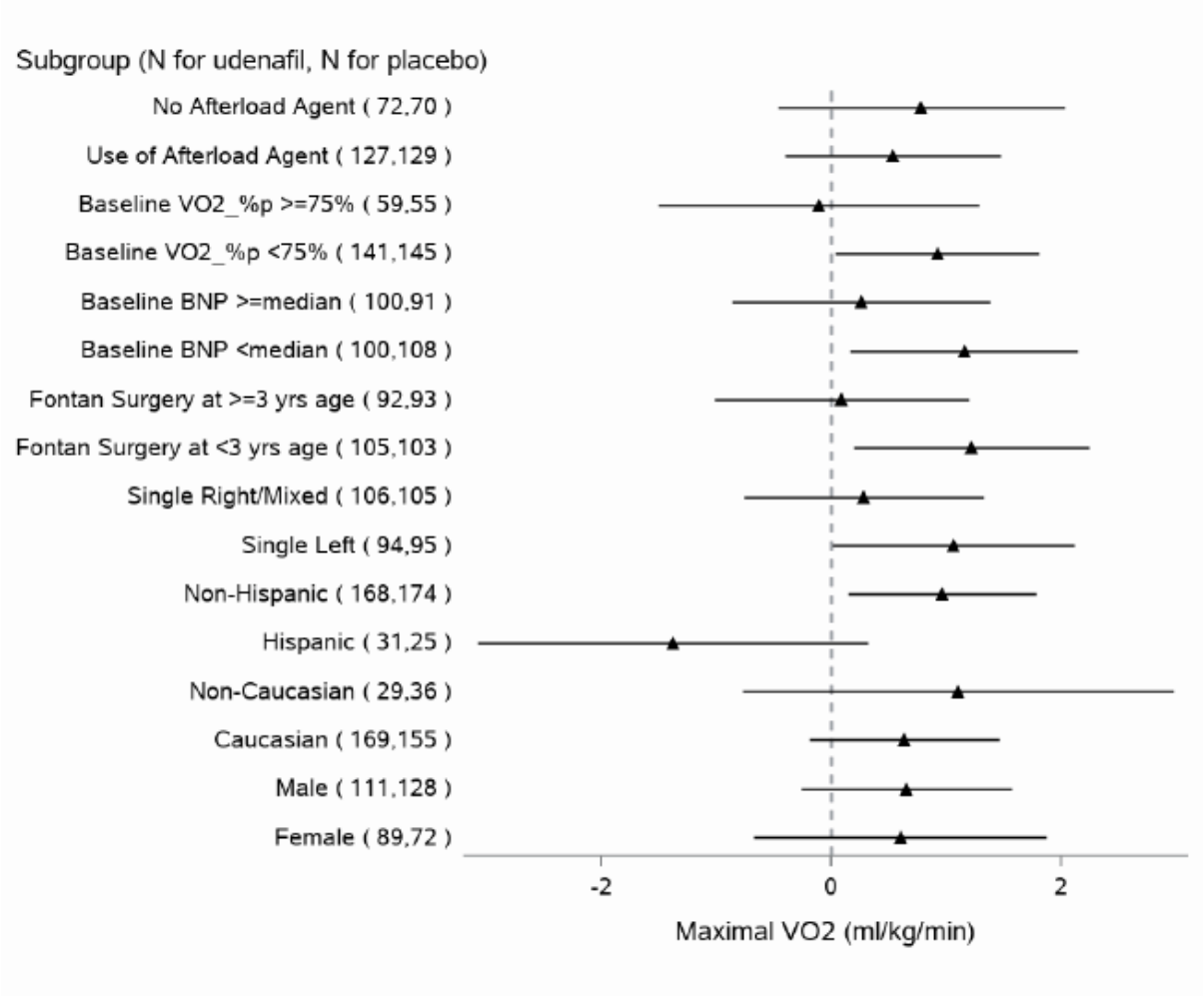
%p=percent predicted; BNP=brain natriuretic peptide; ITT=intent-to-treat; VO_2=minute oxygen consumption; yrs=years
Note: No imputation was performed.
Source: Figure 14.2.1.1.6
Program: f_forestplot

The treatment group difference (udenafil minus placebo) for change in maximal VO_2 (mL/kg/min) from baseline to Week 26 was positive for most subgroups (Figure 3). Positive differences indicate less mean deterioration from baseline for udenafil than for placebo.

Treatment group differences are also presented in mL/kg/min without imputation by gender (Table 14.2.2.1.2.1), race (Table 14.2.2.1.2.2), ethnicity (Table 14.2.2.1.2.3), ventricular morphology (Table 14.2.2.1.2.4), age at Fontan surgery (Table 14.2.2.1.2.5), baseline serum

BNP (Table 14.2.2.1.2.6), percent predicted maximal VO_2 at baseline (Table 14.2.2.1.2.7), and use of afterload reducing agents (Table 14.2.2.1.2.8).

Figure 3: Treatment Group Difference in Mean Maximal VO_2 (mL/kg/min) With 95% Confidence Interval for Change Between Week 26 and Baseline Visits in Subpopulations Using Last Observation Carried Forward (ITT Population)

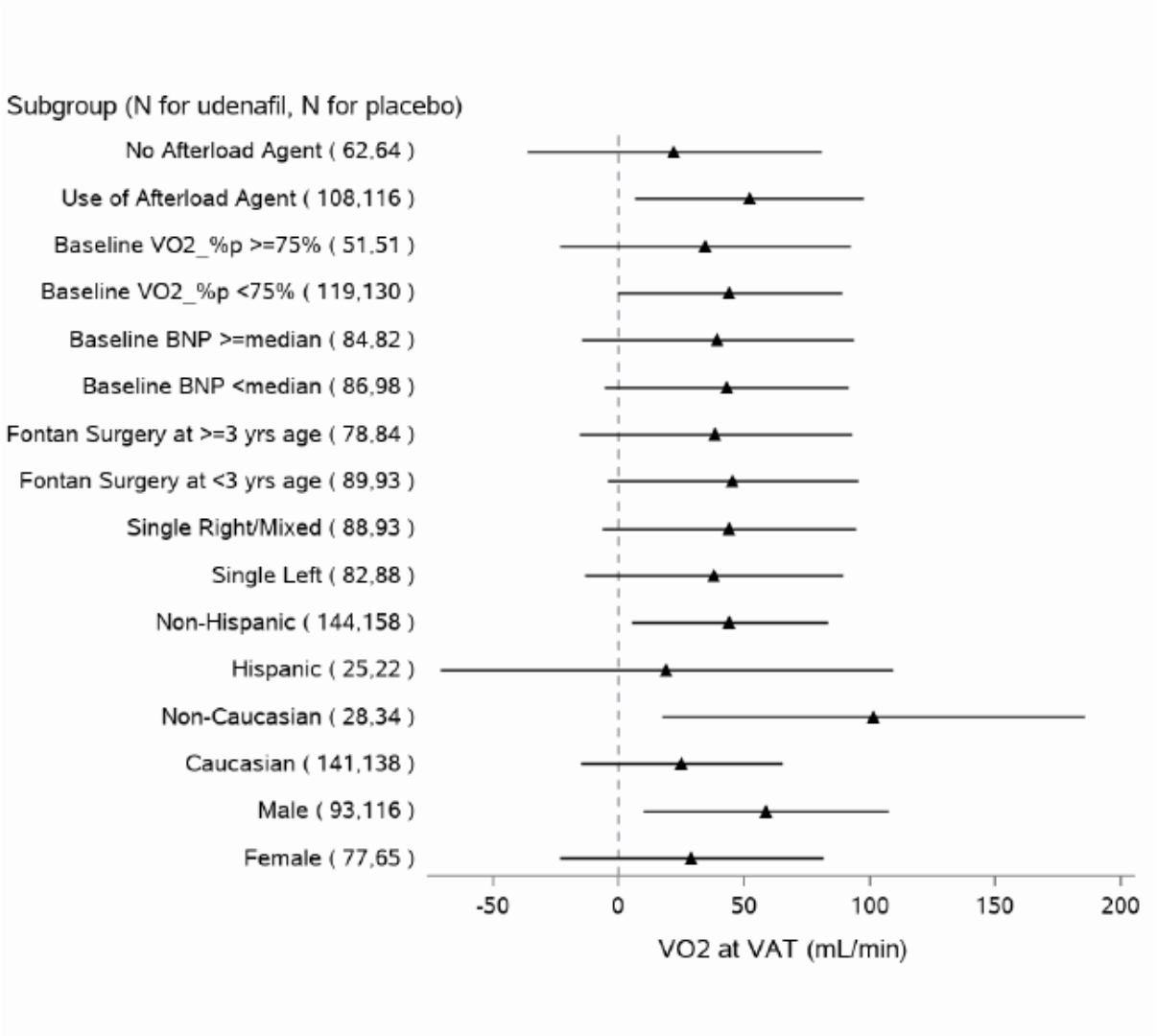


%p=percent predicted; BNP=brain natriuretic peptide; ITT=intent-to-treat; VO_2=minute oxygen consumption; yrs=years
Note: No imputation was performed.
Source: Figure 14.2.1.1.7
Program: f_forestplot

The treatment group difference (udenafil minus placebo) for change in VO_2 at VAT (mL/min) from baseline to Week 26 was positive for all subgroups (Figure 4). Positive differences indicate greater mean improvement from baseline for udenafil than for placebo.

Treatment group differences are also presented in mL/min without imputation by gender (Table 14.2.3.1.2.1), race (Table 14.2.3.1.2.2), ethnicity (Table 14.2.3.1.2.3), ventricular morphology (Table 14.2.3.1.2.4), age at Fontan surgery (Table 14.2.3.1.2.5), baseline serum BNP (Table 14.2.3.1.2.6), percent of predicted maximal VO_2 at baseline (Table 14.2.3.1.2.7), and use of afterload reducing agents (Table 14.2.3.1.2.8).

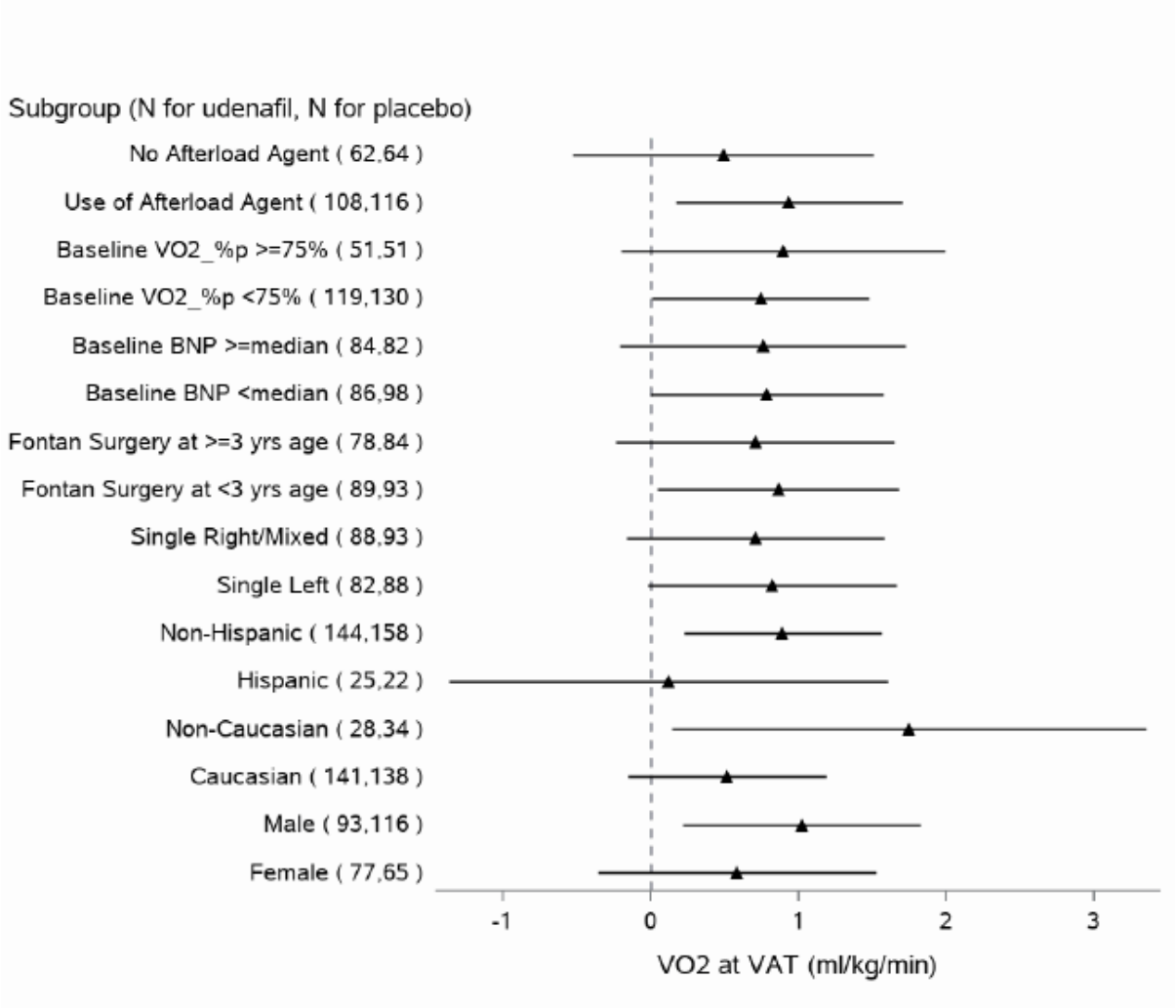
Figure 4: Treatment Group Difference in Mean VO_2 (mL/min) at VAT With 95% Confidence Interval for Change Between Week 26 and Baseline Visits in Subpopulations Using Last Observation Carried Forward (ITT Population)



%p=percent predicted; BNP=brain natriuretic peptide; ITT=intent-to-treat; VAT=ventilatory anaerobic threshold; VO_2=minute oxygen consumption; yrs=years
Note: No imputation was performed. Subjects with unknown race and ethnicity were excluded from the respective analysis.
Source: Figure 14.2.2.1.6
Program: f_forestplot

The treatment group difference (udenafil minus placebo) for change in VO_2 at VAT (mL/kg/min) from baseline to Week 26 was positive for all subgroups (Figure 5). Positive differences indicate less mean deterioration from baseline for udenafil than for placebo.

Figure 5: Treatment Group Difference in Mean VO_2 (mL/kg/min) at VAT With 95% Confidence Interval for Change Between Week 26 and Baseline Visits in Subpopulations Using Last Observation Carried Forward (ITT Population)



%p=percent predicted; BNP=brain natriuretic peptide; ITT=intent-to-treat; VAT=ventilatory anaerobic threshold; VO_2=minute oxygen consumption; yrs=years
Note: No imputation was performed. Subjects with unknown race and ethnicity were excluded from the respective analysis.
Source: Figure 14.2.2.1.7
Program: f_forestplot

11.4.3 Tabulation of Individual Response Data

Tabulations of individual response data are found in Appendix 16.2.

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

Drug dose and drug concentration relationships to response were not assessed.

11.4.5 Drug-Drug and Drug-Disease Interactions

Drug-drug and drug-disease interactions were not assessed.

11.4.6 By-Subject Displays

There were no by-subject displays of individual response to study drug except as provided in the data listings (Appendix 16.2).

11.4.7 Efficacy Conclusions

Key Efficacy Findings

The primary aim of this study was to evaluate the effect of 26 weeks of treatment with udenafil on exercise capacity in adolescents with Fontan physiology. The protocol-specified primary exercise outcome was change in maximal VO_2 and secondary exercise outcomes included change in VO_2 at VAT, change in ventilatory efficiency at VAT, and work rate at VAT. All exercise measures demonstrated a favorable outcome for udenafil relative to placebo.

For maximal VO_2, the udenafil group had a mean increase from baseline to Week 26 compared to a mean decrease in the placebo group (44.40 mL/min versus -3.65 mL/min; p=0.071). When standardized by each subject's body weight, the least squares mean treatment group difference was 0.64 mL/kg/min (p=0.092).

The following secondary efficacy endpoints measured at VAT also indicated greater exercise capacity in the udenafil group than the placebo group at Week 26:

- VO_2 at VAT: Mean increase (improvement) for udenafil as compared to a mean decrease in the placebo group (29.65 mL/min versus -8.01 mL/min; p=0.023). When standardized by each subject's body weight, the least squares mean treatment group difference was 0.78 mL/kg/min (p=0.012).

- VE/VCO_2 at VAT: Greater mean decrease (improvement) for udenafil as compared to placebo (-0.76 versus -0.05; p=0.011).

- Work rate at VAT: Greater mean increase (improvement) for udenafil as compared to placebo (3.46 watts versus 0.31 watts; p=0.029).

An additional efficacy aim evaluated the effect of 26 weeks of treatment with udenafil on the performance of a single ventricle. The primary measure of ventricular performance was change in MPI, which indicated improvement with udenafil versus placebo (-0.02 vs 0.01; p=0.024).

Relative Utility of Maximal VO_2 Versus VO_2 at VAT

The protocol-specified primary endpoint of maximal VO_2 measures overall aerobic capacity and has been shown to be useful as a predictor of cardiac death and hospitalization for heart failure, both in congenital and acquired heart disease. Given the relative ease of obtaining this measure and its utility as a surrogate outcome, maximal VO_2 has been chosen as an endpoint in multiple observational studies and clinical trials. In view of the above, and to be consistent with generally accepted understanding in the pediatric cardiology community, maximal VO_2 was chosen as the primary endpoint for the FUEL trial. An alternative exercise measure, VO_2 at VAT, was also considered during the initial study design, but was designated as a secondary endpoint for 2 reasons: 1) There were more limited relevant data from prior studies to allow for a robust power calculation, and 2) VO_2 at VAT is more difficult to measure precisely, which could lead to data loss and impact statistical power in this rare pediatric disease. The concern about data loss was confirmed in the FUEL trial in which 21% of participants did not have paired data VO_2 at VAT (Table 14.2.3.1.2) versus 5% for maximal VO_2 (Table 14.2.1.1.2).

Despite its utility in most forms of heart disease, recent publications suggest that maximal VO_2 may not be an ideal efficacy measure for interventions in Fontan physiology, particularly for therapies that would improve exercise performance by modification of the PVR. During

exercise, there is a substantial increase in metabolic demand for oxygen delivery and, therefore, cardiac output. In the absence of a sub-pulmonary pump, preload is maintained by the pressure gradient across the pulmonary vascular bed; the difference between CVP and atrial pressure. As exercise intensity increases, CVP must rise to allow for increased transpulmonary blood flow (Qp). Udenafil may modulate this relationship by lowering PVR and therefore allowing for a lower CVP for any given amount of Qp. However, as exercise intensity increases, modification of PVR alone may not be sufficient to allow for the needed increase in cardiac output. Even with optimal pulmonary vasodilation, an increase in CVP is required to provide adequate Qp to keep up with metabolic demand. At the highest levels of exertion, one begins to exceed the physiologic limit of maximal CVP. This physiologic limit, or ceiling, is that point at which exercise is limited by an inability to raise CVP any further.

In a person with a structurally normal heart, there is no physiologic ceiling during exercise related to venous pressure. CVP, which starts at 5 to 7 mmHg, is unchanged during exercise as pulmonary blood flow is driven by the sub-pulmonary right ventricle. In a person who has undergone Fontan palliation and does not have a sub-pulmonary ventricle, CVP starts out much higher (12 to 15 mmHg) and then increases dramatically with exercise. This high pressure cannot be sustained beyond the physiologic ceiling and results in limited ability to maintain ventricular preload and increase cardiac output at higher levels of aerobic exertion. Thus, while pulmonary vasodilators may improve exercise capacity at moderate levels of activity, there is a physiologic limit to their ability to impact performance at levels of exertion approaching the physiologic ceiling. Studies published since the inception of the FUEL trial highlight these unique physiological limitations in the Fontan circulation and point away from the selection of maximal VO_2 as an endpoint for this specific type of congenital heart disease (Goldberg 2021; Navaratnam 2016).

As a consequence of the physiologic limitations associated with Fontan palliation, therapies designed to improve aerobic capacity by decreasing PVR will have their greatest impact at lower levels of aerobic activity and thus lower levels of CVP. VO_2 at VAT is a measure of submaximal exercise that represents the physiologic point at which the metabolic demands of the exercising muscles begin to outstrip the ability of the cardiovascular system to deliver adequate amounts of oxygen to meet those demands. While VO_2 at VAT is more technically difficult to measure than peak VO_2, it has the same association with important morbidities and mortality as maximal VO_2 (Gitt 2002; Malhotra 2016; Tsai 2018). Given the unique features of the Fontan circulation, VO_2 at VAT, despite the challenges associated with data acquisition, is more robust as a surrogate endpoint for this population than maximal VO_2. Given the lack of understanding in the field of this unique physiology at the time of conception of the FUEL trial, the power analysis for maximal VO_2 was predicated on the

impact of alterations in PVR on exercise capacity for those with other forms of heart disease. Although udenafil may have some effect on maximal VO_2, this effect is blunted by the physiologic ceiling of CVP. The expanded understanding of Fontan physiology in recent years has taught that the assumptions informing the selection of maximal VO_2 as the primary endpoint were inaccurate, and that VO_2 at VAT is a more useful endpoint for this unique cohort of patients.

Overall Efficacy Conclusions

In summary, treatment with udenafil for 26 weeks resulted in improvements in exercise capacity, as well as an improvement in the performance of the single ventricle. Although the primary endpoint did not reach statistical significance, new knowledge of the limits of the Fontan circulation explains why this endpoint is an imperfect choice for this circulation. Even with the limitations associated with maximal VO_2, this endpoint showed a clear trend toward improvement that, coupled with the improvement at the anaerobic threshold, speaks to the efficacy of udenafil to improve exercise capacity in this population. Based on the superior exercise capacity and ventricular performance for udenafil as compared to placebo at Week 26, this study achieved its primary clinical objective for a population with no pharmacotherapeutic options.

12 Safety Evaluation

12.1 Extent of Exposure

The mean number of days from first to last dose was 179.8 days in the udenafil group and 182.7 days in the placebo group (Table 23). Mean percent compliance with study drug was 89.92% in the udenafil group and 89.97% in the placebo group. Compliance results are listed by subject in Listing 16.2.5.1.

Table 23: Extent of Exposure and Compliance with Study Drug (Safety Population)

	Udenafil (N=200)	Placebo (N=200)	Total (N=400)
Number of days from first to last dose	(N=200)	(N=200)	(N=400)
Mean (SD)	179.8 (32.23)	182.7 (26.78)	181.3 (29.63)
Median	183.0	183.0	183.0
Minimum, maximum	5, 344	8, 280	5, 344
Percent compliance (%)	(N=174)	(N=185)	(N=359)
Mean (SD)	89.92 (10.283)	89.97 (10.342)	89.94 (10.299)
Median	92.89	93.20	93.09
Minimum, maximum	48.5, 100.0	39.6, 100.0	39.6, 100.0

SD=standard deviation
Source: Table 14.3.1.1
Program: t_14_3_1_1.sas

The mean (standard deviation) udenafil concentration was 174.99 (112.00) ng/mL at 2 hours ± 30 minutes after dosing on Day 1 and 259.19 (166.062) at Week 26 (Table 14.3.1.2). A summary of log-transformed udenafil concentrations is provided in Table 14.3.1.3. The mean (standard deviation) concentration of the DA-8164 metabolite was 74.34 (65.471) ng/mL at 2 hours ± 30 minutes after dosing on Day 1 and 225.59 (161.602) at Week 26 (Table 14.3.1.4). A summary of log-transformed DA-8164 concentrations is provided in Table 14.3.1.5. Concentrations of udenafil and DA-8164 are listed by subject and study visit in Listing 16.2.5.2.

12.2 Adverse Events (AEs)

12.2.1 Brief Summary of Adverse Events

A notably larger percentage (≥5 percentage points) of udenafil-treated than placebo-treated subjects reported at least 1 TEAE (79.0% versus 67.5%) and drug-related TEAE (66.0% versus 42.5%). The incidence of TEAEs of Grade ≥3, serious TEAEs, drug-related serious TEAEs, and TEAEs resulting in temporary discontinuation (identified as drug interrupted in listings) or permanent discontinuation of study drug was similar between treatment groups (Table 24).

Table 24: Overall Summary of Treatment-emergent Adverse Events (Safety Population)

Subjects with ≥1:	Udenafil (N=200) n (%)	Placebo (N=200) n (%)
TEAE	158 (79.0)	135 (67.5)
Drug-related TEAE	132 (66.0)	85 (42.5)
TEAEs of Grade ≥3	10 (5.0)	6 (3.0)
Serious TEAEs	14 (7.0)	10 (5.0)
Drug-related serious TEAEs	4 (2.0)	2 (1.0)
TEAE that led to temporary or permanent discontinuation of study drug	18 (9.0)	13 (6.5)

TEAE=treatment-emergent adverse event
Source: Table 14.3.2
Program: t_14_3_2.sas

12.2.2 Display of Adverse Events

TEAEs reported by ≥5% of subjects in the udenafil group (Table 14.3.5) included headache (39.0%), flushing (14.5%), epistaxis (10.0%), nasopharyngitis (10.0%), nausea (9.5%), dizziness (8.5%), vomiting (7.5%), upper respiratory tract infection (7.0%), erection increased (6.3% of males), spontaneous penile erection (6.3% of males), influenza (5.5%), chest pain (5.0%), pharyngitis streptococcal (5.0%), and rash (5.0%). TEAEs reported by ≥5% of subjects in the placebo group included headache (25.5%), chest pain (9.0%), dizziness (9.0%), upper respiratory tract infection (8.5%), nasopharyngitis (6.5%), flushing (6.0%), and fatigue (5.5%).

A notably greater percentage (≥5 percentage points) of subjects in the udenafil group as compared to the placebo group reported headache (39.0% versus 25.5%), flushing (14.5% versus 6.0%), epistaxis (10.0% versus 3.0%), nausea (9.5% versus 4.5%), and erection increased (6.3% of males versus 0.8% of males) (Table 14.3.5).

Common TEAEs (reported by ≥5% of all subjects) are summarized in Table 25.

Table 25: Most Common (≥5% of All Subjects) Treatment-emergent Adverse Events (Safety Population)

System Organ Class Preferred Term:	Udenafil (N=200) n (%)	Placebo (N=200) n (%)
Subjects with ≥1 TEAE	158 (79.0)	135 (67.5)
Gastrointestinal disorders	55 (27.5)	33 (16.5)
Nausea	19 (9.5)	9 (4.5)
Vomiting	15 (7.5)	6 (3.0)
General disorders and administration site conditions	33 (16.5)	39 (19.5)
Chest pain	10 (5.0)	18 (9.0)
Infections and infestations	69 (34.5)	60 (30.0)
Nasopharyngitis	20 (10.0)	13 (6.5)
Upper respiratory tract infection	14 (7.0)	17 (8.5)
Nervous system disorders	95 (47.5)	65 (32.5)
Dizziness	17 (8.5)	18 (9.0)
Headache	78 (39.0)	51 (25.5)
Respiratory, thoracic and mediastinal disorders	45 (22.5)	29 (14.5)
Epistaxis	20 (10.0)	6 (3.0)
Vascular disorders	32 (16.0)	14 (7.0)
Flushing	29 (14.5)	12 (6.0)

TEAE=treatment-emergent adverse event
Source: Table 14.3.3 and Table 14.3.5
Program: 14_3_ae_tables.sas

12.2.2.1 Treatment-emergent Adverse Events by Intensity

Most TEAEs were mild or moderate in intensity (Table 14.3.6A and Table 14.3.6B). Severe TEAEs were reported for 10 (5.0%) udenafil-treated subjects and 6 (3.0%) placebo-treated subjects (Table 14.3.6C); no life-threatening TEAEs were reported in either treatment group (Listing 16.2.7.1). Dizziness was the only severe TEAE reported by >1 subject (2 placebo subjects).

Four drug-related, severe TEAEs were reported in the udenafil group (Listing 16.2.7.1): diplegia (Subject 130008), retinal vascular occlusion (Subject 140015), anxiety

(Subject 210003), and palpitations (Subject 530013). Study drug was withdrawn for Subjects 130008 and 140015 (Table 35), and study drug was interrupted for Subject 530013 (Table 36). Two drug-related, severe TEAEs were reported in the placebo group: dizziness and syncope for Subject 420006. No change was made to study drug dosing. None of the other severe TEAEs were considered related to study drug.

12.2.2.2 Treatment-emergent Adverse Events Related to Study Drug

Drug-related TEAEs reported by ≥5% of subjects in the udenafil group (Table 14.3.7A) included headache (38.0%), flushing (14.5%), epistaxis (7.5%), dizziness (6.5%), nausea (6.5%), erection increased (6.3% of males), and spontaneous penile erection (6.3% of males). Drug-related TEAEs reported by ≥5% of subjects in the placebo group included headache (22.0%), dizziness (7.0%), and flushing (6.0%). A notably greater percentage (≥5 percentage points) of subjects in the udenafil group as compared to the placebo group reported drug-related headache (38.0% versus 22.0%), flushing (14.5% versus 6.0%), erection increased (6.3% of males versus 0.8% of males), spontaneous penile erection (6.3% of males versus 0.8% of males), and epistaxis (7.5% versus 1.5%).

Common drug-related TEAEs (reported by ≥2% of all subjects) are summarized in Table 26. TEAEs considered not related to study drug by the Investigator are summarized in Table 14.3.7B.

Table 26: Most Common (≥2% of All Subjects) Treatment-emergent Adverse Events Related to Study Drug (Safety Population)

System Organ Class Preferred Term:	Udenafil (N=200) n (%)	Placebo (N=200) n (%)
Subjects with ≥1 TEAE related to study drug	132 (66.0)	85 (42.5)
Gastrointestinal disorders	30 (15.0)	19 (9.5)
Abdominal pain upper	6 (3.0)	6 (3.0)
Nausea	13 (6.5)	7 (3.5)
General disorders and administration site conditions	19 (9.5)	15 (7.5)
Chest pain	3 (1.5)	6 (3.0)
Fatigue	5 (2.5)	7 (3.5)
Infections and infestations	14 (7.0)	7 (3.5)
Upper respiratory tract infection	7 (3.5)	3 (1.5)
Nervous system disorders	89 (44.5)	55 (27.5)
Dizziness	13 (6.5)	14 (7.0)
Headache	76 (38.0)	44 (22.0)
Migraine	5 (2.5)	4 (2.0)
Reproductive system and breast disorders	15 (7.5)	3 (1.5)
Erection increased[a]	7 (6.3)	1 (0.8)
Spontaneous penile erection[a]	7 (6.3)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	27 (13.5)	13 (6.5)
Epistaxis	15 (7.5)	3 (1.5)
Nasal congestion	5 (2.5)	4 (2.0)
Vascular disorders	31 (15.5)	13 (6.5)
Flushing	29 (14.5)	12 (6.0)

TEAE=treatment-emergent adverse event
a Percentage calculated based on number of male subjects in each treatment group.
Source: Table 14.3.7A
Program: 14_3_ae_tables.sas

12.2.3 Analysis of Adverse Events

In this section, the most common TEAEs (reported by ≥5% of all subjects) are summarized for subgroups defined by gender (female, male), race (Caucasian/White, non-Caucasian/White), ethnicity (Hispanic or Latino/Latina, not Hispanic or Latino/Latina), age (tertiles at baseline), and weight (tertiles at baseline). A notable difference between groups is defined as ≥5 percentage points.

Gender

In the udenafil group, there was a notable increase among females versus males for chest pain (7.9% versus 2.7%). The incidence of common TEAEs is summarized separately for females and males in Table 27.

Among females (N=161), a notably greater percentage of subjects in the udenafil group experienced headache (40.4% udenafil, 26.4% placebo) and flushing (16.9% udenafil, 9.7% placebo). A notably greater percentage of subjects in the placebo group experienced dizziness (7.9% udenafil, 13.9% placebo).

Among males (N=239), a notably greater percentage of subjects in the udenafil group experienced nausea (10.8% udenafil, 2.3% placebo), vomiting (9.0% udenafil, 3.1% placebo), nasopharyngitis (11.7% udenafil, 6.3% placebo), headache (37.8% udenafil, 25.0% placebo), epistaxis (9.9% udenafil, 0.8% placebo), and flushing (12.6% udenafil, 3.9% placebo). A notably greater percentage of subjects in the placebo group experienced chest pain (2.7% udenafil, 10.2% placebo). In addition, the incidence of erection increased was greater in the udenafil group (6.3% udenafil, 0.8% placebo; Table 14.3.5).

Race

In the udenafil group, there was a notable increase among Caucasians/Whites versus non-Caucasians/Whites for dizziness (9.5% versus 3.4%). There was a notable decrease among Caucasians/Whites versus non-Caucasians/Whites for nausea (8.3% versus 13.8%), nasopharyngitis (8.9% versus 17.2%), and headache (37.9% versus 44.8%). Given the disparity in sample sizes between the racial groups, these differences are difficult to interpret. The incidence of common TEAEs is summarized separately for Caucasians/Whites and non-Caucasians/Whites in Table 28.

Among Caucasians/Whites (N=324), a notably greater percentage of subjects in the udenafil group experienced headache (37.9% udenafil, 27.1% placebo), epistaxis (9.5% udenafil, 3.2% placebo), and flushing (14.8% udenafil, 7.1% placebo).

Among non-Caucasians/Whites (N=65), a notably greater percentage of subjects in the udenafil group experienced nausea (13.8% udenafil, 5.6% placebo), vomiting (10.3% udenafil, 0 placebo), nasopharyngitis (17.2% udenafil, 8.3% placebo), headache (44.8% udenafil, 16.7% placebo), epistaxis (13.8% udenafil, 2.8% placebo), and flushing (13.8% udenafil, 2.8% placebo).

Ethnicity

In the udenafil group, there was a notable increase among Hispanic or Latino/Latina subjects versus subjects not Hispanic or Latino/Latina for vomiting (12.9% versus 6.5%). There was a notable increase among subjects not Hispanic or Latino/Latina versus Hispanic or Latino/Latina subjects for upper respiratory tract infection (8.3% versus 0) and flushing (15.5% versus 9.7%). Given the disparity in sample sizes between the ethnic groups, these differences are difficult to interpret. The incidence of common TEAEs is summarized separately for Hispanic or Latino/Latina subjects and subjects not Hispanic or Latino/Latina in Table 29.

Among Hispanic or Latino/Latina subjects (N=56), a notably greater percentage of subjects in the udenafil group experienced nausea (12.9% udenafil, 4.0% placebo), nasopharyngitis (9.7% udenafil, 0 placebo), headache (41.9% udenafil, 28.0% placebo) and epistaxis (9.7% udenafil, 0 placebo). A notably greater percentage of subjects in the placebo group experienced chest pain (3.2% udenafil, 24.0% placebo).

Among subjects not Hispanic or Latino/Latina (N=342), a notably greater percentage of subjects in the udenafil group experienced headache (38.1% udenafil, 25.3% placebo), epistaxis (10.1% udenafil, 3.4% placebo), and flushing (15.5% udenafil, 5.7% placebo).

Age at Baseline

For age at baseline, comparisons are focused on the extremes of the age range (ie, low tertile versus high tertile). In the udenafil group, there was a notable increase among subjects within the high age tertile versus subjects in the low age tertile for nasopharyngitis (15.2% versus 8.3%). There was a notable increase among subjects in the low age tertile versus subjects in the high age tertile for flushing (18.1% versus 12.1%). The incidence of common TEAEs is summarized separately for baseline age tertiles in Table 30.

Within the low age tertile (N=133), a notably greater percentage of subjects in the udenafil group experienced dizziness (11.1% udenafil, 4.9% placebo), headache (38.9% udenafil,

29.5% placebo), epistaxis (12.5% udenafil, 4.9% placebo), and flushing (18.1% udenafil, 1.6% placebo).

Within the high age tertile (N=133), a notably greater percentage of subjects in the udenafil group experienced nausea (9.1% udenafil, 0 placebo), vomiting (10.6% udenafil, 1.5% placebo), nasopharyngitis (15.2% udenafil, 0 placebo), headache (36.4% udenafil, 25.4% placebo), and flushing (12.1% udenafil, 6.0% placebo). A notably greater percentage of subjects in the placebo group experienced chest pain (6.1% udenafil, 11.9% placebo) and upper respiratory tract infection (6.1% udenafil, 11.9% placebo).

Among males in the high age tertile, a greater percentage of subjects in the udenafil group than the placebo group reported erection increased and spontaneous penile erection (7.9% versus 0 for each event; Table 14.3.9C).

Weight at Baseline

For weight at baseline, comparisons are focused on the extremes of the weight range (ie, low tertile versus high tertile). In the udenafil group, there was a notable increase in the low weight tertile versus the high weight tertile for the percentage of subjects experiencing nausea (9.3% versus 3.5%), headache (41.3% versus 28.1%), and flushing (16.0% versus 10.5%). The incidence of common TEAEs is summarized separately for baseline weight tertiles in Table 31.

Within the low weight tertile (N=134), a notably greater percentage of subjects in the udenafil group experienced headache (41.3% udenafil, 23.7% placebo), epistaxis (13.3% udenafil, 3.4% placebo), and flushing (16.0% udenafil, 1.7% placebo). A notably greater percentage of subjects in the placebo group experienced chest pain (2.7% udenafil, 8.5% placebo) and dizziness (6.7% udenafil, 11.9% placebo).

Within the high weight tertile (N=134), a notably greater percentage of subjects in the udenafil group experienced vomiting (8.8% udenafil, 2.6% placebo). A notably greater percentage of subjects in the placebo group experienced chest pain (1.8% udenafil, 7.8% placebo).

Among male subjects, a greater percentage of subjects in the udenafil group than the placebo group reported erection increased and spontaneous penile erection in the low weight tertile (5.0% versus 0 and 10.0% versus 3.0%, respectively; Table 14.3.8A) and in the high weight tertile (5.6% versus 0 and 8.3% versus 0, respectively; Table 14.3.8C).

Table 27: Most Common (≥5% of All Subjects) Treatment-emergent Adverse Events by Gender (Safety Population)

	Male Subjects (N=239)			Female Subjects (N=161)		
Preferred Term:	**Udenafil (N=111) n (%)**	**Placebo (N=128) n (%)**	**Total (N=239) n (%)**	**Udenafil (N=89) n (%)**	**Placebo (N=72) n (%)**	**Total (N=161) n (%)**
Nausea	12 (10.8)	3 (2.3)	15 (6.3)	7 (7.9)	6 (8.3)	13 (8.1)
Vomiting	10 (9.0)	4 (3.1)	14 (5.9)	5 (5.6)	2 (2.8)	7 (4.3)
Chest pain	3 (2.7)	13 (10.2)	16 (6.7)	7 (7.9)	5 (6.9)	12 (7.5)
Nasopharyngitis	13 (11.7)	8 (6.3)	21 (8.8)	7 (7.9)	5 (6.9)	12 (7.5)
Upper respiratory tract infection	7 (6.3)	8 (6.3)	15 (6.3)	7 (7.9)	9 (12.5)	16 (9.9)
Dizziness	10 (9.0)	8 (6.3)	18 (7.5)	7 (7.9)	10 (13.9)	17 (10.6)
Headache	42 (37.8)	32 (25.0)	74 (31.0)	36 (40.4)	19 (26.4)	55 (34.2)
Epistaxis	11 (9.9)	1 (0.8)	12 (5.0)	9 (10.1)	5 (6.9)	14 (8.7)
Flushing	14 (12.6)	5 (3.9)	19 (7.9)	15 (16.9)	7 (9.7)	22 (13.7)

Source: Table 14.3.4A and Table 14.3.4B
Program: 14_3_ae_tables.sas

Table 28: Most Common (≥5% of All Subjects) Treatment-emergent Adverse Events by Race Category (Safety Population)

	Caucasian/White Subjects (N=324)			Non-Caucasian/White Subjects (N=65)		
Preferred Term:	**Udenafil (N=169) n (%)**	**Placebo (N=155) n (%)**	**Total (N=324) n (%)**	**Udenafil (N=29) n (%)**	**Placebo (N=36) n (%)**	**Total (N=65) n (%)**
Nausea	14 (8.3)	6 (3.9)	20 (6.2)	4 (13.8)	2 (5.6)	6 (9.2)
Vomiting	11 (6.5)	4 (2.6)	15 (4.6)	3 (10.3)	0	3 (4.6)
Chest pain	8 (4.7)	14 (9.0)	22 (6.8)	2 (6.9)	2 (5.6)	4 (6.2)
Nasopharyngitis	15 (8.9)	10 (6.5)	25 (7.7)	5 (17.2)	3 (8.3)	8 (12.3)
Upper respiratory tract infection	13 (7.7)	17 (11.0)	30 (9.3)	1 (3.4)	0	1 (1.5)
Dizziness	16 (9.5)	12 (7.7)	28 (8.6)	1 (3.4)	3 (8.3)	4 (6.2)
Headache	64 (37.9)	42 (27.1)	106 (32.7)	13 (44.8)	6 (16.7)	19 (29.2)
Epistaxis	16 (9.5)	5 (3.2)	21 (6.5)	4 (13.8)	1 (2.8)	5 (7.7)
Flushing	25 (14.8)	11 (7.1)	36 (11.1)	4 (13.8)	1 (2.8)	5 (7.7)

Note: Summary excludes 11 subjects of unknown or not reported race.
Source: Table 14.3.4C and Table 14.3.4D
Program: 14_3_ae_tables.sas

Table 29: Most Common (≥5% of All Subjects) Treatment-emergent Adverse Events by Ethnicity Category (Safety Population)

	Hispanic or Latino/Latina Subjects (N=56)			Not Hispanic or Latino/Latina Subjects (N=342)		
Preferred Term:	**Udenafil (N=31) n (%)**	**Placebo (N=25) n (%)**	**Total (N=56) n (%)**	**Udenafil (N=168) n (%)**	**Placebo (N=174) n (%)**	**Total (N=342) n (%)**
Nausea	4 (12.9)	1 (4.0)	5 (8.9)	15 (8.9)	8 (4.6)	23 (6.7)
Vomiting	4 (12.9)	3 (12.0)	7 (12.5)	11 (6.5)	3 (1.7)	14 (4.1)
Chest pain	1 (3.2)	6 (24.0)	7 (12.5)	9 (5.4)	12 (6.9)	21 (6.1)
Nasopharyngitis	3 (9.7)	0	3 (5.4)	17 (10.1)	13 (7.5)	30 (8.8)
Upper respiratory tract infection	0	0	0	14 (8.3)	17 (9.8)	31 (9.1)
Dizziness	2 (6.5)	2 (8.0)	4 (7.1)	15 (8.9)	16 (9.2)	31 (9.1)
Headache	13 (41.9)	7 (28.0)	20 (35.7)	64 (38.1)	44 (25.3)	108 (31.6)
Epistaxis	3 (9.7)	0	3 (5.4)	17 (10.1)	6 (3.4)	23 (6.7)
Flushing	3 (9.7)	2 (8.0)	5 (8.9)	26 (15.5)	10 (5.7)	36 (10.5)

Note: Summary excludes 2 subjects of unknown ethnicity.
Source: Table 14.3.4E and Table 14.3.4F
Program: 14_3_ae_tables.sas

Table 30: Most Common (≥5% of All Subjects) Treatment-emergent Adverse Events by Baseline Age Tertile (Safety Population)

	Low Age Tertile (N=133)			Medium Age Tertile (N=134)			High Age Tertile (N=133)		
Preferred Term:	**Udenafil (N=72) n (%)**	**Placebo (N=61) n (%)**	**Total (N=133) n (%)**	**Udenafil (N=62) n (%)**	**Placebo (N=72) n (%)**	**Total (N=134) n (%)**	**Udenafil (N=66) n (%)**	**Placebo (N=67) n (%)**	**Total (N=133) n (%)**
Nausea	9 (12.5)	5 (8.2)	14 (10.5)	4 (6.5)	4 (5.6)	8 (6.0)	6 (9.1)	0	6 (4.5)
Vomiting	6 (8.3)	3 (4.9)	9 (6.8)	2 (3.2)	2 (2.8)	4 (3.0)	7 (10.6)	1 (1.5)	8 (6.0)
Chest pain	3 (4.2)	2 (3.3)	5 (3.8)	3 (4.8)	8 (11.1)	11 (8.2)	4 (6.1)	8 (11.9)	12 (9.0)
Nasopharyngitis	6 (8.3)	7 (11.5)	13 (9.8)	4 (6.5)	6 (8.3)	10 (7.5)	10 (15.2)	0	10 (7.5)
Upper respiratory tract infection	7 (9.7)	6 (9.8)	13 (9.8)	3 (4.8)	3 (4.2)	6 (4.5)	4 (6.1)	8 (11.9)	12 (9.0)
Dizziness	8 (11.1)	3 (4.9)	11 (8.3)	3 (4.8)	8 (11.1)	11 (8.2)	6 (9.1)	7 (10.4)	13 (9.8)
Headache	28 (38.9)	18 (29.5)	46 (34.6)	26 (41.9)	16 (22.2)	42 (31.3)	24 (36.4)	17 (25.4)	41 (30.8)
Epistaxis	9 (12.5)	3 (4.9)	12 (9.0)	6 (9.7)	1 (1.4)	7 (5.2)	5 (7.6)	2 (3.0)	7 (5.3)
Flushing	13 (18.1)	1 (1.6)	14 (10.5)	8 (12.9)	7 (9.7)	15 (11.2)	8 (12.1)	4 (6.0)	12 (9.0)

Source: Table 14.3.9A, Table 14.3.9B, and Table 14.3.9C
Program: 14_3_ae_tables.sas

Table 31: Most Common (≥5% of All Subjects) Treatment-emergent Adverse Events by Baseline Weight Tertile (Safety Population)

	Low Weight Tertile (N=134)			Medium Weight Tertile (N=132)			High Weight Tertile (N=134)		
Preferred Term:	**Udenafil (N=75) n (%)**	**Placebo (N=59) n (%)**	**Total (N=134) n (%)**	**Udenafil (N=68) n (%)**	**Placebo (N=64) n (%)**	**Total (N=132) n (%)**	**Udenafil (N=57) n (%)**	**Placebo (N=77) n (%)**	**Total (N=134) n (%)**
Nausea	7 (9.3)	4 (6.8)	11 (8.2)	10 (14.7)	1 (1.6)	11 (8.3)	2 (3.5)	4 (5.2)	6 (4.5)
Vomiting	6 (8.0)	2 (3.4)	8 (6.0)	4 (5.9)	2 (3.1)	6 (4.5)	5 (8.8)	2 (2.6)	7 (5.2)
Chest pain	2 (2.7)	5 (8.5)	7 (5.2)	7 (10.3)	7 (10.9)	14 (10.6)	1 (1.8)	6 (7.8)	7 (5.2)
Nasopharyngitis	5 (6.7)	5 (8.5)	10 (7.5)	11 (16.2)	4 (6.3)	15 (11.4)	4 (7.0)	4 (5.2)	8 (6.0)
Upper respiratory tract infection	7 (9.3)	7 (11.9)	14 (10.4)	3 (4.4)	4 (6.3)	7 (5.3)	4 (7.0)	6 (7.8)	10 (7.5)
Dizziness	5 (6.7)	7 (11.9)	12 (9.0)	6 (8.8)	4 (6.3)	10 (7.6)	6 (10.5)	7 (9.1)	13 (9.7)
Headache	31 (41.3)	14 (23.7)	45 (33.6)	31 (45.6)	16 (25.0)	47 (35.6)	16 (28.1)	21 (27.3)	37 (27.6)
Epistaxis	10 (13.3)	2 (3.4)	12 (9.0)	5 (7.4)	0	5 (3.8)	5 (8.8)	4 (5.2)	9 (6.7)
Flushing	12 (16.0)	1 (1.7)	13 (9.7)	11 (16.2)	4 (6.3)	15 (11.4)	6 (10.5)	7 (9.1)	13 (9.7)

Source: Table 14.3.8A, Table 14.3.8B, and Table 14.3.8C
Program: 14_3_ae_tables.sas

12.2.4 Listing of Adverse Events by Subject

All adverse events are listed by individual subject in Listing 16.2.7.1.

12.3 Deaths, other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1.1 Deaths

No subject died during the study (Table 14.3.18).

12.3.1.2 Other Serious Adverse Events

At least 1 serious TEAE was reported by 14 (7.0%) subjects in the udenafil group and 10 (5.0%) subjects in the placebo group (Table 32). Serious TEAEs reported by at least 2 subjects included chest pain (2 udenafil subjects), influenza (2 udenafil subjects), syncope (2 placebo subjects) and dyspnoea (1 udenafil subject and 1 placebo subject). All other serious TEAEs were reported by a single subject each.

Hospitalization was reported for 23 subjects (14 udenafil, 9 placebo) during the study (Table 14.3.18). Hospitalized subjects are identified in Listing 16.2.7.3. No transplants were reported during the study (Table 14.3.18). Tabular summaries of transplants and hospitalizations by weight tertile are provided in Table 14.3.19A, Table 14.3.19B, and Table 14.3.19C. Tabular summaries of transplants and hospitalizations by age tertile are provided in Table 14.3.20A, Table 14.3.20B, and Table 14.3.20C.

Table 32: Serious Treatment-emergent Adverse Events Reported for ≥2 Subjects (Safety Population)

System Organ Class Preferred Term	Udenafil (N=200) n (%)	Placebo (N=200) n (%)
Subjects with ≥1 serious TEAE	14 (7.0)	10 (5.0)
General disorders and administration site conditions	2 (1.0)	1 (0.5)
Chest pain	2 (1.0)	0
Infections and infestations	2 (1.0)	3 (1.5)
Influenza	2 (1.0)	0
Nervous system disorders	2 (1.0)	5 (2.5)
Syncope	0	2 (1.0)
Respiratory, thoracic and mediastinal disorders	3 (1.5)	1 (0.5)
Dyspnoea	1 (0.5)	1 (0.5)

TEAE=treatment-emergent adverse event
Source: Table 14.3.10
Program: 14_3_ae_tables.sas

Six subjects (4 udenafil, 2 placebo) had serious TEAEs that were considered related to study drug (Table 14.3.11A). In the udenafil group, drug-related serious TEAEs included anxiety and bronchospasm reported in 1 subject and diplegia, retinal vascular occlusion, and palpitations reported in 1 subject each. In the placebo group, 2 subjects experienced a drug-related serious TEAE of syncope. Serious adverse events considered not related to study drug by the Investigator are summarized in Table 14.3.11B. All serious TEAEs are listed in Table 33.

A short description is provided below for each drug-related serious TEAE.

A 15-year-old male (Subject 130008) in the udenafil group experienced a serious TEAE of diplegia (verbatim: inability to move legs) on Day 158. The event was severe in intensity and considered possibly related to study drug per the Investigator. Mild asthenia was also reported. The subject had missed approximately 1 week of study drug when he forgot to take his study medication on vacation. Two days after resuming study drug, the subject did not feel well and complained of an upset stomach, sore throat, and feeling weak. Later that day, the subject was admitted to the hospital after reporting he was unable to move his legs. He also developed sudden onset lower extremity paresthesia, weakness of his left arm, and experienced an episode of urinary incontinence. No abnormalities were observed on vital signs or laboratory assessments. Magnetic resonance imaging of the brain, neck, thoracic and lumbar spine were unremarkable. No treatment was administered for the event and the

subject was discharged from the hospital 2 days later with no confirmed clinical diagnosis. The subject was discontinued from study drug due to the event. At a follow-up visit performed 1 day after discharge, the subject reported the event had resolved and was fully back to normal.

A 14-year-old female (Subject 140015) in the udenafil group experienced a serious TEAE of retinal vascular occlusion (verbatim: retinal vascular occlusion) on Day 128. The event was severe in intensity, considered possibly related to study drug per the Investigator, and resulted in permanent discontinuation of study drug. The subject was hospitalized after experiencing vision loss in the right eye characterized as sudden onset of blurry vision and gray spots, progressing to complete gray within 45 minutes. Ophthalmic exam revealed right afferent pupillary defect (4+) and slit lamp examination showed blurred optic disc margins and slightly pallid temporal region without blood and massive whitening with cherry red spot. The retina had narrowed arterioles with mild 'boxcarring' with question of a small cilioretinal artery that did not extend to the macula. The subject was not receiving anticoagulant therapy at the time of the event due to past history of hemoptysis; however, evaluation for a hypercoagulable state showed no significant findings. Additional evaluations including computed tomography scan of the head, brain magnetic resonance imaging, magnetic resonance angiography, and duplex studies of the carotid artery and lower extremities were unremarkable. The subject was discharged with a diagnosis of complete occlusion of the central retinal artery without evidence of thromboembolism. The vision loss was permanent and was considered stable at the date of her final study telephone call.

An 18-year-old female (Subject 210003) in the udenafil group experienced serious TEAEs of anxiety (verbatim: anxiety) and bronchospasm (verbatim: bronchospasm). The anxiety event began on Day 35, was severe in intensity and considered possibly related to study drug per the Investigator; the event was noted as resolved on Day 40. The bronchospasm event began on Day 86, was of moderate intensity, and considered possibly related to study drug per the Investigator; this event was ongoing at study completion. Salbutamol was prescribed on Day 86. The subject also experienced nonserious TEAEs of mild dyspnoea and mild upper respiratory tract infection during the study.

A 19-year-old male (Subject 530013) in the udenafil group experienced a serious TEAE of palpitations (verbatim: palpitation) that began on Day 45. The event was severe in intensity and considered probably related to study drug per the Investigator. The subject was admitted to the hospital for evaluation of palpitations, following an episode of pyrexia and gastrointestinal symptoms. Study drug was interrupted for the event. The event was treated

with amiodarone for 1 day, then supportive care with furosemide, spironolactone and intravenous fluids was administered. The event was noted as resolved on Study Day 47.

An 18-year-old female (Subject 420006) in the placebo group experienced a serious TEAE of syncope (verbatim: fainted) on Day 117. The event was severe in intensity and considered possibly related to study drug per the Investigator. The subject presented to the hospital emergency department after fainting at work and having recovered consciousness within several minutes. The subject had been non-compliant with study drug dosing for 4 days prior to the event. Vital signs showed no orthostatic changes and laboratory tests were within normal limits with exception of slight decreases in hemoglobin and hematocrit. Electrocardiogram results were similar to those observed on an electrocardiogram performed 3 months prior. No intravenous fluids or medications were administered for treatment of the event and the subject was discharged, with the event noted as resolved the same day.

A 15-year-old female (Subject 490002) in the placebo group experienced a serious TEAE of syncope (verbatim: syncope/vasovagal) on Day 29. The event was moderate in intensity and considered possibly related to study drug per the Investigator. The subject was hospitalized following a syncopal episode upon standing, characterized as loss of consciousness with concurrent cyanosis. Evaluation showed orthostatic changes in vital signs. No abnormalities were observed on chest x-ray or telemetry. Treatment included intravenous fluids and ibuprofen. The event was noted as resolved the same day.

Table 33: Listing of Serious Treatment-emergent Adverse Events

Treatment/ Subject Number	Gender	Age (Years)	Preferred Term	Day of Onset	Relationship to Study Drug	Intensity	Study Drug Action Taken
Udenafil							
110006	Female	14.6	Dyspnoea	263	Not related	Severe	None reported
		14.6	Chest pain	263	Not related	Severe	None reported
110008	Male	13.8	Influenza	254	Not related	Severe	None reported
120004	Female	16.2	Gastrointestinal haemorrhage	134	Not related	Severe	Dose not changed
		16.2	Protein-losing gastroenteropathy	134	Not related	Severe	Dose not changed
		16.2	Protein-losing gastroenteropathy	159	Not related	Severe	Drug withdrawn
130008	Male	15.2	Diplegia	158	Possibly related	Severe	Drug withdrawn
140004	Female	17.0	Paralysis	104	Not related	Moderate	Drug interrupted
140015	Female	14.5	Retinal vascular occlusion	128	Possibly related	Severe	Drug withdrawn
140031	Female	12.8	Arrhythmia	130	Not related	Severe	Dose not changed
		12.8	Respiratory failure	144	Not related	Severe	Dose not changed
210003	Female	18.3	Anxiety	35	Possibly related	Severe	Dose not changed
		18.5	Bronchospasm	86	Possibly related	Moderate	Dose not changed
210012	Male	12.8	Intestinal obstruction	93	Not related	Moderate	Drug interrupted
		13.0	Influenza	159	Not related	Moderate	Dose not changed
270018	Female	12.9	Menorrhagia	79	Not related	Severe	None reported

Table 33: Listing of Serious Treatment-emergent Adverse Events (Continued)

Treatment/ Subject Number	Gender	Age (Years)	Preferred Term	Day of Onset	Relationship to Study Drug	Intensity	Study Drug Action Taken
Udenafil (continued)							
330003	Male	19.1	Renal failure	58	Not related	Severe	Drug interrupted
		19.1	Toxicity to various agents	58	Not related	Severe	Drug interrupted
		19.2	Bipolar I disorder	96	Not related	Severe	Dose not changed
480013	Female	18.7	Chest pain	148	Not related	Mild	Drug interrupted
530013	Male	19.1	Palpitations	45	Probably related	Severe	Drug interrupted
		19.1	Venous stenosis	48	Not related	Severe	Dose not changed
540010	Male	18.1	Anal haemorrhage	103	Not related	Moderate	Dose not changed
		18.1	Constipation	103	Not related	Moderate	Dose not changed
Placebo							
120017	Female	19.1	Migraine	65	Not related	Moderate	Dose not changed
140040	Male	13.5	Cardiac failure	2	Not related	Severe	Dose not changed
170012	Male	15.9	Appendicitis	185	Not related	Severe	Drug interrupted
170018	Male	12.2	Transient ischaemic attack	66	Not related	Moderate	Drug interrupted
230006	Female	18.9	Fatigue	23	Not related	Severe	Dose not changed
		19.0	Abdominal pain	76	Not related	Mild	Dose not changed
420003	Male	17.0	Dyspnoea	133	Not related	Moderate	Dose not changed
		17.0	Dizziness	133	Not related	Severe	Dose not changed
420006	Female	18.4	Syncope	117	Possibly related	Severe	Dose not changed
		18.5	Depression	155	Not related	Severe	Dose not changed
480008	Male	18.9	Pharyngitis	165	Not related	Moderate	Dose not changed
490002	Female	15.4	Syncope	29	Possibly related	Moderate	Dose not changed
500001	Male	15.0	Viral upper respiratory tract infection	57	Not related	Moderate	Dose not changed

Source: Listing 16.2.7.4

12.3.1.3 Other Significant Adverse Events

12.3.1.3.1 Adverse Events Leading to Discontinuation of Study Drug

At least 1 TEAE leading to temporary or permanent discontinuation of study drug was reported by 18 (9.0%) subjects in the udenafil group and 13 (6.5%) subjects in the placebo group (Table 34). TEAEs leading to temporary or permanent discontinuation of study drug reported by at least 2 subjects included headache (3 udenafil subjects and 3 placebo subjects), nausea (2 udenafil subjects), vomiting (2 udenafil subjects), abdominal pain upper (2 placebo subjects), and gastroenteritis viral (1 udenafil subject and 1 placebo subject). All other TEAEs leading to temporary or permanent discontinuation of study drug were reported by a single subject each.

Table 34: Treatment-emergent Adverse Events Leading to Temporary or Permanent Discontinuation of Study Drug That Were Reported for ≥2 Subjects (Safety Population)

System Organ Class Preferred Term	Udenafil (N=200) n (%)	Placebo (N=200) n (%)
Subjects with ≥1 TEAE resulting in discontinuation of study drug	18 (9.0)	13 (6.5)
Gastrointestinal disorders	5 (2.5)	4 (2.0)
Abdominal pain upper	0	2 (1.0)
Nausea	2 (1.0)	0
Vomiting	2 (1.0)	0
Infections and infestations	2 (1.0)	3 (1.5)
Gastroenteritis viral	1 (0.5)	1 (0.5)
Nervous system disorders	6 (3.0)	5 (2.5)
Headache	3 (1.5)	3 (1.5)

TEAE=treatment-emergent adverse event
Source: Table 14.3.14
Program: 14_3_ae_tables.sas

Of the 18 subjects in the udenafil group, 13 subjects had ≥1 TEAE that resulted in interruption of study drug, 4 subjects (120004, 130008, 140015, and 170013) had ≥1 TEAE that resulted in permanent discontinuation of study drug, and 1 subject (160011) had 1 TEAE each that resulted in interruption and permanent discontinuation (Listing 16.2.7.1). Of the 13 subjects in the placebo group, 9 subjects had ≥1 TEAE that resulted in interruption of

study drug and 4 subjects (270020, 310009, 390001, and 470001) had ≥1 TEAE that resulted in permanent discontinuation of study drug (Listing 16.2.7.1). A listing of TEAEs that resulted in permanent discontinuation from study drug is provided in Table 35, and a listing of TEAEs that resulted in interruption of study drug is provided in Table 36.

Table 35: Listing of Treatment-emergent Adverse Events Resulting in Permanent Discontinuation of Study Drug

Treatment/ Subject Number	Gender	Age (Years)	Preferred Term	Day of Onset	Relationship to Study Drug	Intensity	Serious
Udenafil							
120004	Female	16.2	Protein-losing gastroenteropathy	159	Not related	Severe	Yes
130008	Male	15.2	Diplegia	158	Possibly related	Severe	Yes
		15.2	Asthenia	158	Possibly related	Mild	No
140015	Female	14.5	Retinal vascular occlusion	128	Possibly related	Severe	Yes
160011	Male	13.7	Headache	118	Possibly related	Moderate	No
170013	Female	18.0	Visual field defect	25	Possibly related	Mild	No
Placebo							
270020	Male	13.9	Swollen tongue	8	Probably related	Moderate	No
		13.9	Urticaria	8	Probably related	Moderate	No
310009	Female	18.9	Headache	31	Probably related	Moderate	No
390001	Male	15.8	Eye pain	99	Possibly related	Mild	No
470001	Female	12.6	Headache	1	Possibly related	Mild	No

Source: Listing 16.2.7.1

Table 36: Listing of Treatment-emergent Adverse Events Resulting in Interruption of Study Drug

Treatment/ Subject Number	Gender	Age (Years)	Preferred Term	Day of Onset	Relationship to Study Drug	Intensity	Serious
Udenafil							
140004	Female	16.8	Hypoaesthesia	22	Possibly related	Moderate	No
		17.0	Paralysis	104	Not related	Moderate	Yes
140037	Female	15.0	Headache	2	Probably related	Mild	No
160011	Male	13.3	Headache	3	Possibly related	Mild	No
180007	Male	14.5	Nausea	9	Not related	Mild	No
		14.5	Vomiting	9	Not related	Mild	No
180008	Female	13.1	Nausea	2	Not related	Mild	No
210005	Male	13.8	Gastroenteritis viral	51	Not related	Mild	No
210012	Male	12.8	Intestinal obstruction	93	Not related	Moderate	Yes
270006	Female	15.5	Headache	1	Possibly related	Mild	No
310005	Male	13.2	Vomiting	2	Possibly related	Moderate	No
330003	Male	19.1	Toxicity to various agents	58	Not related	Severe	Yes
		19.1	Renal failure	58	Not related	Severe	Yes
470002	Male	14.8	Belligerence	8	Possibly related	Mild	No
470010	Male	19.1	Candida infection	63	Not related	Mild	No
480013	Female	18.7	Chest pain	148	Not related	Mild	Yes
530013	Male	19.1	Palpitations	45	Probably related	Severe	Yes

Table 36: Listing of Treatment-emergent Adverse Events Resulting in Interruption of Study Drug (Continued)

Treatment/ Subject Number	Gender	Age (Years)	Preferred Term	Day of Onset	Relationship to Study Drug	Intensity	Serious
Placebo							
140001	Female	17.6	Gastroenteritis viral	155	Not related	Mild	No
140038	Male	13.5	Pyrexia	163	Not related	Mild	No
160004	Female	16.6	Dizziness	2	Possibly related	Mild	No
160005	Female	14.5	Conjunctivitis	23	Possibly related	Moderate	No
170012	Male	15.9	Appendicitis	185	Not related	Severe	Yes
170018	Male	12.2	Transient ischaemic attack	66	Not related	Moderate	Yes
210008	Female	13.0	Diarrhoea	2	Possibly related	Mild	No
310006	Female	14.4	Epistaxis	1	Possibly related	Mild	No
		14.5	Abdominal pain upper	12	Possibly related	Mild	No
330006	Male	16.9	Headache	23	Not related	Mild	No
		16.9	Abdominal pain upper	23	Not related	Mild	No

Source: Listing 16.2.7.1

12.3.1.3.2 Adverse Events of Special Interest

Adverse events of hypotension (eg, blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, hypotension, procedural hypotension), loss of consciousness, dizziness (eg, dizziness, dizziness exertional, procedural dizziness), presyncope, and syncope (syncope, syncope vasovagal) were identified in the SAP for separate summarization. Hypotension, dizziness, and syncope have been reported with other PDE-5 inhibitors (Pfizer 2017); loss of consciousness can be associated with these events.

At least 1 TEAE of special interest was reported by 18 (9.0%) subjects in the udenafil group and 19 (9.5%) subjects in the placebo group (Table 37). The incidence of individual TEAEs was similar between treatment groups.

Table 37: Number (Percent) of Subjects Reporting Treatment-emergent Adverse Events of Special Interest (Safety Population)

System Organ Class Preferred Term	Udenafil (N=200) n (%)	Placebo (N=200) n (%)
Subjects with ≥1 TEAE of special interest	18 (9.0)	19 (9.5)
Dizziness	17 (8.5)	18 (9.0)
Loss of consciousness	0	1 (0.5)
Syncope	1 (0.5)	3 (1.5)

TEAE=treatment-emergent adverse event
Source: Table 14.3.15
Program: 14_3_ae_tables.sas

The incidence of TEAEs of special interest was generally similar across age and weight tertiles. Tabular summaries of TEAEs of special interest by weight tertile are provided in Table 14.3.16A, Table 14.3.16B, and Table 14.3.16C. Tabular summaries of TEAEs of special interest by age tertile are provided in Table 14.3.17A, Table 14.3.17B, and Table 14.3.17C.

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

Individual subject narratives for serious TEAEs, TEAEs resulting in discontinuation of study drug, and TEAEs of special interest are provided in Section 14.3.3.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

No subject died during the study. At least 1 serious TEAE was reported by 14 (7.0%) subjects in the udenafil group and 10 (5.0%) subjects in the placebo group. No individual serious TEAE was reported by >2 subjects in either treatment group. Hospitalization was reported for 23 subjects (14 udenafil, 9 placebo) during the study. No transplants were reported.

At least 1 TEAE leading to temporary or permanent discontinuation of study drug was reported by 18 (9.0%) subjects in the udenafil group and 13 (6.5%) subjects in the placebo group. Headache was the only TEAE leading to temporary or permanent discontinuation of study drug reported by >2 subjects in either treatment group (3 subjects each in the udenafil and placebo groups).

The percentage of subjects reporting at least 1 serious TEAE is summarized across subgroups defined by baseline age and weight tertiles in Table 38. No specific serious TEAE was reported for more than 2 subjects each in the udenafil group. Due to low number of subjects reporting specific serious TEAEs, summaries of individual serious TEAEs across subgroups are not meaningful.

Table 38: Number (Percent) of Subjects Reporting at Least 1 Serious Treatment-emergent Adverse Event by Age and Weight Tertiles (Safety Population)

Subgroup:	Udenafil (N=200) n/N (%)	Placebo (N=200) n/N (%)
Age at baseline		
Low tertile	6/72 (8.3)	2/61 (3.3)
Medium tertile	2/62 (3.2)	3/72 (4.2)
High tertile	6/66 (9.1)	5/67 (7.5)
Weight at baseline		
Low tertile	7/75 (9.3)	1/59 (1.7)
Medium tertile	3/68 (4.4)	5/64 (7.8)
High tertile	4/57 (7.0)	4/77 (5.2)

n=number of subjects with at least 1 serious adverse event; N=number of subjects in subgroup;
%=(n divided by N) × 100

Source: Table 14.3.12A, Table 14.3.12B, Table 14.3.12C, Table 14.3.13A, Table 14.3.13B, and Table 14.3.13C
Program: T_14_3_ae_tables.sas

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Results for alanine aminotransferase, aspartate aminotransferase, and creatinine are listed by subject and study visit in Listing 16.2.8.2.

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values Over Time

Mean changes in alanine aminotransferase, aspartate aminotransferase, and creatinine from baseline to Week 26 were small and similar between treatment groups (Table 39).

Table 39: Changes in Safety Laboratory Values from Baseline to Week 26 (Safety Population)

	Udenafil (N=200)		Placebo (N=200)		LS Mean
	N	Mean (SD)	N	Mean (SD)	Difference (SE)
ALT (U/L)					
Baseline[a]	200	35.07 (14.287)	200	34.88 (14.552)	0.20 (1.444)
Week 26	189	35.08 (14.282)	192	35.93 (14.925)	-0.84 (1.499)
Difference, Week 26 – baseline	189	-0.34 (11.104)	192	0.73 (10.126)	-1.01 (1.018)
AST (U/L)					
Baseline[a]	200	32.57 (12.091)	200	32.15 (12.050)	0.41 (1.206)
Week 26	189	32.58 (11.542)	193	33.06 (15.350)	-0.48 (1.390)
Difference, Week 26 – baseline	189	-0.08 (9.154)	193	0.75 (14.538)	-0.70 (1.156)
Creatinine (mg/dL)					
Baseline[a]	200	0.68 (0.142)	200	0.72 (0.141)	-0.03 (0.014)
Week 26	189	0.74 (0.162)	192	0.76 (0.149)	-0.02 (0.016)
Difference, Week 26 – baseline	189	0.06 (0.098)	192	0.04 (0.113)	0.01 (0.011)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; LS=least squares; SD=standard deviation; SE=standard error
a Baseline value was defined as the last assessment on or before dosing at baseline visit.
Source: Table 14.3.21
Program: T_14_3_21.sas

12.4.2.2 Individual Subject Changes

The percentages of subjects with a shift in alanine aminotransferase, aspartate aminotransferase, or creatinine from within normal limits at baseline to above the upper limit of normal at postbaseline were low and similar between treatment groups (Table 40). No subject met criteria for Grade 3 toxicity (>5 × upper limit of normal) for alanine aminotransferase or aspartate aminotransferase (Listing 16.2.8.2).

Table 40: Shifts from Within Normal Limits at Baseline to Above Upper Limit of Normal at Postbaseline (Safety Population)

Laboratory Parameter	Udenafil n/N (%)	Placebo n/N (%)
ALT	2/189 (1.1)	1/192 (0.5)
AST	5/189 (2.6)	4/193 (2.1)
Creatinine	0/189	0/192

ALT=alanine aminotransferase; AST=aspartate aminotransferase; n=number of subjects with at least 1 shift; N=number of subjects with data at baseline and postbaseline; %=(n divided by N) × 100

Source: Table 14.3.22
Program: T_14_3_22.sas

12.4.2.3 Individual Clinically Significant Abnormalities

The following TEAEs were reported for changes in hepatic enzymes.

- Alanine aminotransferase increased and aspartate aminotransferase decreased: 1 subject in the udenafil group (Subject 390005) had values of 74 and 57 U/L, respectively, at baseline and values of 46 and 43 U/L, respectively, at Week 26. All values were within the normal reference range.

- Alanine aminotransferase increased: 2 subjects in the placebo group. Subject 310006 had values of 26 U/L at baseline and 38 U/L at Week 26. Subject 500001 had values of 56 U/L at baseline and 63 U/L at Week 26. All reported values were within the normal reference range for both subjects.

No TEAEs were reported for changes in creatinine.

12.5 Vital Signs, Physical Findings and other Observations Related to Safety

Mean changes from baseline in blood pressure and heart rate were small and generally similar between treatment groups (Table 41). Statistically significant treatment group differences were observed for change in diastolic blood pressure from baseline to Week 2 and to Week 26, with greater decreases in the udenafil group.

Table 41: Changes in Blood Pressure and Heart Rate from Baseline to Week 2, Week 13, and Week 26 (Safety Population)

	Udenafil (N=200)	Placebo (N=200)	p-value[a]
Systolic blood pressure (mmHg)			
Baseline[b]	n=200	n=200	
Mean (standard deviation)	112.32 (12.136)	113.21 (12.887)	0.477
Week 2 – baseline[c]	n=154	n=155	
Mean (standard deviation)	-1.34 (14.846)	-0.64 (15.424)	0.682
Week 13 – baseline[c]	n=131	n=143	
Mean (standard deviation)	-1.15 (13.000)	-1.26 (13.978)	0.948
Week 26 – baseline	n=189	n=190	
Mean (standard deviation)	-1.90 (12.166)	-0.49 (11.535)	0.246
Diastolic blood pressure (mmHg)			
Baseline[b]	n=200	n=200	
Mean (standard deviation)	68.39 (9.508)	69.30 (10.142)	0.355
Week 2 – baseline[c]	n=154	n=154	
Mean (standard deviation)	-4.34 (12.113)	-1.46 (12.398)	0.040
Week 13 – baseline[c]	n=131	n=143	
Mean (standard deviation)	-3.75 (11.374)	-1.95 (12.695)	0.220
Week 26 – baseline	n=189	n=190	
Mean (standard deviation)	-3.01 (9.644)	0.05 (10.696)	0.004
Heart rate (bpm)			
Baseline[b]	n=200	n=200	
Mean (standard deviation)	87.52 (15.253)	88.12 (14.128)	0.683
Week 2 – baseline[c]	n=154	n=155	
Mean (standard deviation)	-6.90 (13.464)	-8.30 (14.810)	0.385
Week 13 – baseline[c]	n=131	n=143	
Mean (standard deviation)	-6.94 (15.606)	-7.83 (14.230)	0.621
Week 26 – baseline	n=189	n=190	
Mean (standard deviation)	-1.06 (12.725)	-1.02 (12.448)	0.977

a P-value was assessed using analysis of variance with fixed factor for treatment group.
b Last pre-drug administration measurement.
c Collection of blood pressure and heart rate at Week 2 and Week 13 was stopped in the middle of the study and removed from the protocol version 3.0 (31 August 2017).
Source: Table 14.3.23
Program: T_14_3_23.sas

The percentages of subjects with potentially clinically significant vital sign values pre-6-minute walk and post-6-minute walk on Day 1 were small and similar between treatment groups. Potentially clinically significant vital sign changes on Day 1 are

summarized in Table 42. There were no TEAEs for blood pressure or heart rate associated with these changes. Vital sign results for individual subjects are presented in Listing 16.2.8.1.

Table 42: Potentially Clinically Significant Vital Sign Changes on Day 1 (Safety Population)

Vital Sign Time Point	Udenafil (N=200)	Placebo (N=200)
Low systolic blood pressure, n (%) with postdose value ≤80 mmHg and decreased ≥20 mmHg from value before dosing		
Pre-6MWT[a]	0	0
Post-6MWT[a]	0	0
≥1 event at either time point	0	0
High systolic blood pressure, n (%) with postdose value ≥140 mmHg and increased ≥20 mmHg from value before dosing		
Pre-6MWT[a]	0	0
Post-6MWT[a]	11 (5.5)	8 (4.0)
≥1 event at either time point	11 (5.5)	8 (4.0)
Low diastolic blood pressure, n (%) with postdose value ≤50 mmHg and decreased ≥15 mmHg from value before dosing		
Pre-6MWT[a]	2 (1.0)	2 (1.0)
Post-6MWT[a]	2 (1.0)	3 (1.5)
≥1 event at either time point	4 (2.0)	4 (2.0)
High diastolic blood pressure, n (%) with postdose value ≥100 mmHg and increased ≥15 mmHg from value before dosing		
Pre-6MWT[a]	0	1 (0.5)
Post-6MWT[a]	1 (0.5)	0
≥1 event at either time point	1 (0.5)	1 (0.5)
Low heart rate, n (%) with postdose value ≤45 bpm and decreased ≥15 bpm from value before dosing		
Pre-6MWT[a]	0	0
Post-6MWT[a]	1 (0.5)	0
≥1 event at either time point	1 (0.5)	0
High heart rate, n (%) with postdose value ≥130 bpm and increased ≥15 bpm from value before dosing		
Pre-6MWT[a]	0	0
Post-6MWT[a]	5 (2.5)	4 (2.0)
≥1 event at either time point	5 (2.5)	4 (2.0)

6MWT=6-minute walk test
a Approximately 2 hours after first drug administration.
Source: Table 14.3.24
Program: T_14_3_24.sas

12.6 Safety Conclusions

A notably larger percentage (≥5 percentage points) of udenafil-treated than placebo-treated subjects reported at least 1 TEAE (79.0% versus 67.5%) and at least 1 drug-related TEAE (66.0% versus 42.5%). The incidence of TEAEs of Grade ≥3, serious TEAEs, drug-related serious TEAEs, and TEAEs resulting in temporary or permanent discontinuation of study drug was similar between treatment groups.

A notably greater percentage (≥5 percentage points) of subjects in the udenafil group as compared to the placebo group reported headache (39.0% versus 25.5%), flushing (14.5% versus 6.0%), epistaxis (10.0% versus 3.0%), nausea (9.5% versus 4.5%), and erection increased (6.3% of males versus 0.8% of males).

There were no clinically important differences in the TEAE profile among subgroups defined by gender (female, male), race (Caucasian/White, non-Caucasian/White), ethnicity (Hispanic or Latino/Latina, not Hispanic or Latino/Latina), age (tertiles at baseline), and weight (tertiles at baseline).

Severe TEAEs were reported for 10 (5.0%) udenafil-treated subjects and 6 (3.0%) placebo-treated subjects; no life-threatening TEAEs were reported in either treatment group. Dizziness was the only severe TEAE reported by >1 subject (2 placebo subjects).

No subject died during the study. At least 1 serious TEAE was reported by 14 (7.0%) subjects in the udenafil group and 10 (5.0%) subjects in the placebo group. No individual serious TEAE was reported by >2 subjects in either treatment group. Hospitalization was reported for 23 subjects (14 udenafil, 9 placebo) during the study. No transplants were reported.

At least 1 TEAE leading to temporary or permanent discontinuation of study drug was reported by 18 (9.0%) subjects in the udenafil group and 13 (6.5%) subjects in the placebo group. Headache was the only TEAE leading to temporary or permanent discontinuation of study drug reported by >2 subjects in either treatment group (3 subjects each in the udenafil and placebo groups).

There were no clinically important treatment group differences for clinical laboratory findings and vital signs.

Overall, udenafil was safe and well tolerated in this study.

13 Discussion and Overall Conclusions

The primary aim of this study was to evaluate the effect of 26 weeks of treatment with udenafil on exercise capacity in adolescents with Fontan physiology. The protocol-specified primary exercise outcome was change in maximal VO_2 and secondary exercise outcomes included change in VO_2 at VAT, change in ventilatory efficiency at VAT, and work rate at VAT. All exercise measures demonstrated a favorable outcome for udenafil relative to placebo.

For maximal VO_2, the udenafil group had a mean increase from baseline to Week 26 compared to a mean decrease in the placebo group (44.40 mL/min versus -3.65 mL/min; p=0.071). When standardized by each subject's body weight, the least squares mean treatment group difference was 0.64 mL/kg/min (p=0.092).

The following secondary efficacy endpoints measured at VAT also indicated greater exercise capacity in the udenafil group than the placebo group at Week 26:

- VO_2 at VAT: Mean increase (improvement) for udenafil as compared to a mean decrease in the placebo group (29.65 mL/min versus -8.01 mL/min; p=0.023). When standardized by each subject's body weight, the least squares mean treatment group difference was 0.78 mL/kg/min (p=0.012).

- VE/VCO_2 at VAT: Greater mean decrease (improvement) for udenafil as compared to placebo (-0.76 versus -0.05; p=0.011).

- Work rate at VAT: Greater mean increase (improvement) for udenafil as compared to placebo (3.46 watts versus 0.31 watts; p=0.029).

An additional efficacy aim evaluated the effect of 26 weeks of treatment with udenafil on the performance of a single ventricle. The primary measure of ventricular performance was change in MPI, which indicated improvement with udenafil versus placebo (-0.02 versus 0.01; p=0.024).

Common TEAEs with a notably greater incidence (≥5 percentage points) in the udenafil group as compared to the placebo group included headache, flushing, epistaxis, nausea, and erection increased (in males). These events have been reported with other PDE-5 inhibitors (Pfizer 2017).

There were no clinically important differences in the TEAE profile among subgroups defined by gender (female, male), race (Caucasian/White, non-Caucasian/White), ethnicity (Hispanic

or Latino/Latina, not Hispanic or Latino/Latina), age (tertiles at baseline), and weight (tertiles at baseline).

The incidence of TEAEs of Grade ≥3, serious TEAEs, drug-related serious TEAEs, and TEAEs resulting in temporary or permanent discontinuation of study drug was similar between treatment groups. No subject died during the study. No individual serious TEAE was reported by >2 subjects in either treatment group. Hospitalization was reported for 23 subjects (14 udenafil, 9 placebo) during the study.

There were no clinically important treatment group differences for clinical laboratory findings and vital signs. Overall, udenafil was safe and well tolerated in this study.

In summary, this study achieved its primary clinical objectives by demonstrating that udenafil administered orally at 87.5 mg BID for 26 weeks led to improved exercise capacity as compared to placebo in adolescents with Fontan physiology. In addition, myocardial performance was improved in the group treated with udenafil.

14 Tables, Figures and Graphs Referred to but not Included in the Text

14.1 Demographic Data

14.2 Efficacy Data

14.3 Safety Data

14.3.1 Displays of Adverse Events

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

14.3.3 Narratives of Deaths, other Serious and Certain other Significant Adverse Events

14.3.4 Abnormal Laboratory Value and Medication Listings (Each Subject)

15 Reference List

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