A PHASE III SAFETY EXTENSION STUDY OF UDENAFIL IN ADOLESCENTS WITH SINGLE VENTRICLE PHYSIOLOGY AFTER FONTAN PALLIATION

(FUEL EXTENSION)

Funded by The National Heart, Lung, and Blood Institute, NIH/DHHS and Mezzion Pharma Co. Ltd.

Protocol Number: PHN-Udenafil-03

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APPROVALS:

Mezzion Pharma Co. Ltd DocuSigned by: Jim Yeager 11B7B168769C44A... Date 23 November 2020
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Version History		
Version Number	Version Date	Comment(s)
Version 1.0	20-Jan-2016	SPA Re-submission
Version 2.0	04-May-2016	Updated per FDA recommendations for FUEL
Version 3.0	31-Aug-2017	Conversion of visits 2 and 3 to telephone visits, and removal of vital sign measurements at those time points; Addition of inclusion criterion #4 and exclusion criterion #26
Version 4.0	19-Apr-2018	Addition of optional Heart Monitoring; updated shipping of drug resupply; extension of follow-up period; addition of S. Korean in-person visits at weeks 2 and 13. Clarification of exclusion criteria #16. Pregnancy testing at every in-person visit.
Version 5.0	10-Jun-2019	Extension of follow-up to maximum of 36 months
Version 6.0	30-Oct-2020	Extension of follow-up to maximum of 48 months; Telephone call schedule after Week 52 completion updated to quarterly calls; Removal of South Korean sites which were never activated

TABLE OF REVISIONS

March 9, 2016

Location of Change	*Change from*	*Changed to*	*Comment*
-----	-----	-----	Special Protocol Agreement Submission January 27, 2016

May 4, 2016

Location of Change	*Change from*	*Changed to*	*Comment*
-----	-----	-----	Special Protocol Agreement Resubmission May 17, 2016

August 31, 2017

Location of Change	*Change from*	*Changed to*	*Comment*
Title Page	To be determined	Brian Feingold, MD, MS, FAHA University of Pittsburgh School of Medicine Tel: 412-692-5541	A Medical Monitor was identified for the study
Section 2 Protocol Synopsis and Section 7.1 Subject Inclusion Critiera	-----	4. Current anti-platelet or anticoagulant therapy	Inclusion criterion added requiring potential participants be on anti-platelet or anticoagulant therapy to be eligible for the study.

Section 2 Protocol Synopsis and Section 7.2: Subject Exclusion Criteria	-----	26. History of clinically significant thromboembolic event, as adjudicated by study Investigators that may put the subject at increased risk of a subsequent event while participating in the study.	Exclusion criterion added excluding potential participants if they have a history of clinically significant thromboembolic events.
Section 6 Trial Design	-----	-----	Figure 1 was updated to reflect changes in schedule of events
Section 6.4 Study Visits	-----	-----	This section was updated to reflect changes in the schedule of events: removal of in-person visits at weeks 2 and 13; addition of telephone contacts at weeks 2 and 13
Section 6.4, Table 1: Schedule of Events	In-Person Visits (Screening/Baseline, Weeks 2, 13) Telephone Call Visits (Day 1, Weeks 1, 3, 4, 8, 17, 21, 30, 34, 39, 43, 47)	In-Person Visits (Screening/Baseline, Week 52) Telephone Call Visits (Weeks 1, 2, 3, 4, 8, 13, 17, 21, 30, 34, 39, 43, 47)	Conversion of visits 2 and 3 to telephone visits, Removal of vital sign assessments at those time points
Throughout the document (Title page, footer)	May 4, 2016	August 31, 2017	Administrative edits (i.e., protocol date was updated)

April 19, 2018

Location of Change	*Change from*	*Changed to*	*Comment*
1. Protocol Signature Page	"Section 7.2.2"	"Section 9.2.4"	Updated section that identifies reporting serious adverse events
Exclusion Criteria #16	Known intolerance to oral Udenafil.	Known intolerance, including hypersensitivity or allergy history, to oral udenafil or any components of the investigational product.	Clarification for S. Korean Ministry of Food and Drug Safety
Efficacy Measurements	-	Explore the impact of udenafil on atrial and ventricular premature beats and arrhythmia burden – optional for a subset of new participants.	Heart monitoring measurement option for new participants
6.3.2 Measures of Secondary Aims (Pharmacodynamics)	-----	Arrhythmia Burden: Number of premature atrial and/or ventricular beats as a percentage of total beats over the course of heart-rhythm monitoring while on study drug compared to baseline. Measure the occurrence of	Updated secondary measurements to include the heart rhythm monitoring option

		atrial or ventricular arrhythmias, including duration and speed, and comparison to baseline.	
6.4 Study Visits #1 FUEL participants	"The safety labs for FUEL will be accepted as meeting the inclusion criteria for FUEL extension."	"Pregnancy testing for OLE will be done at every in-person visit via a urine or serum pregnancy test for female participants. If the pregnancy test is positive all further testing will be stopped, the patient will not be enrolled into the trial and the result will be conveyed to the subject and/or guardians by the site-principal investigator in accordance with local IRB procedures."	Female participants will have pregnancy testing at any in-person visit.
6.4 Study Visits #6 FUEL participants	-----	Baseline Visit: Heart Rhythm Monitoring procedures added to protocol (see details in section 6.4)	Updated to include optional heart rhythm monitoring application for FUEL Extensionparticipants who were not in FUEL
6.4 Study Visits #6 NON-FUEL participants	-----	Baseline Visit: Heart Rhythm Monitoring procedures added to protocol (see details in section 6.4)	Updated to include optional heart rhythm monitoring application for NON-FUEL participants resulting in splitting baseline visit into 2 days. Day 1 of 2 description
6.4 Study Visits #7	-----	Follow-Up Visit: Heart Rhythm Monitoring procedures added to protocol (see details in section 6.4)	Updated to include Follow-up and the 2nd application of the heart rhythm monitoring at baseline visit day 2 of 2
8.3 Procedures for Monitoring Subject Adherence	"Every 2 months" and "...a 2 month ..."	"Each subject will receive via traceable courier a resupply of study medication."	Updated to remove limitation for resupply as a result of the conversion of two mid-study, in-person visits to phone calls
9.1 Recording and Reporting Adverse Events	"The contacts at weeks 2 and 13 will be in person visits during which adverse events will be assessed."	-----	Updated to reflect the replacement of in person visits at weeks 2 and 13 to telephone calls (US/Canada). Adverse events are captured at all telephone encounters. (see Table 1)
13.1 Potential Risks	-----	Heart Monitor The patch which secures the monitor to the skin may result in	Updated to include potential risk of heart monitor patch on the skin

		local skin irritation or discomfort.	
2. Protocol Synopsis – Study Duration	Approximately 12-15 months (recruitment plus study procedures and follow up phone calls).	Approximately 12-15 months (recruitment plus study procedures and follow up phone calls). The trial may be extended by up to an additional 12-15 months for those opting to continue for a second year.	Adding an option for a second year on open label udenafil for those subjects interested in remaining on drug to allow for more robust safety data capture.
4.2 Secondary Aims	--	Secondary Aim 5: Evaluate the safety of udenafil (87.5 mg bid) in adolescents with Fontan physiology over an additional 12 months.	Updated to include a new secondary aim designed to allow for safety data collection over a longer time period.
6.1 Overview	This study is a 12-month (52 week) safety extension study to supplement the FUEL Phase III clinical trial…	This study is a 12-month (52 week) safety extension study, with an option for up to an additional 12 months, to supplement the FUEL Phase III clinical trial…	Updated to reflect the addition of an option for a second year.
Figure 1 Trial Schema	-	Included the Option 2 in the schema	Context illustrating option 2 within the study schema
Figure 1 Trial Schema	-	Heart monitor (optional)	Included the option of heart monitoring for non-FUEL participants
6.4 Study Visits	--	Option for additional up to 12 months	Added a section detailing the opportunity to participate in FUEL-Extension for up to an additional 12 months.
<u>Telephone Contact (Between Baseline and Week 52)</u>	-	"[South Korean sites will call at weeks 1, 3, 4, 8, 17, 21, 30, 34, 39, 43, 47]"	South Korea has alternate call cycles due to in-person visits at weeks 2 and 13.
Table 1 Schedule of Events	-	Post Week 52 Option 2	Added monthly telephone call schedule for AE assessments

Table 1 Schedule of Events	-	serum or urine pregnancy test at baseline visit for FUEL participant	pregnancy testing at any in-person visit.
5.3 Rationale for the Study	-	(with an option to extend for up to an additional 12 months)	Addition of the extension of up to 12 months.
9.1 Safety Considerations and Monitoring	-	If the subject is continuing into the extension of up to an additional 12 months the site study coordinator will contact each subject monthly until the subject discontinues study drug.	Added statement of safety monitoring for study drug extension of up to 12 months.
9.2.2 Classification of Adverse Events	CTCAE Version 4 MedDRA 12.1 Version 4.0	CTCAE and MedDRA	Current versions of CTCAE and MedDRA are used as they are updated and reelase
10.1 Primary Aim – Safety	...over 12 months of the extension trial ...	…over the duration of the extension trial…	To include the option for up to an additional 12 months
Throughout the document (Title page, footer)	August 31, 2017	April 19, 2018	Administrative edits (i.e., protocol date was updated)

June 10, 2019

Location of Change	*Change from*	*Changed to*	*Comment*
2. Protocol Synopsis – Study Duration	Approximately 12-15 months (recruitment plus study procedures and follow up phone calls). The trial may be extended by up to an additional 12-15 months for those opting to continue for a second year.	Approximately 12-15 months (recruitment plus study procedures and follow up phone calls). The trial may be extended by up to an additional 24-27 months for those opting to continue for additional follow-up.	Adding an option for a third year on open label udenafil for those subjects interested in remaining on drug to allow for more robust safety data capture.
4.2 Secondary Aims	Secondary Aim 5: Evaluate the safety of udenafil (87.5 mg bid) in adolescents with Fontan physiology over an additional 12 months (study months 12-24).	Secondary Aim 5: Evaluate the safety of udenafil (87.5 mg bid) in adolescents with Fontan physiology over an additional 12 months (study months 12-36).	Updated to include additional 12 months of follow-up
5.3 Rationale for the Study 6.1 Study Overview Study 6.4 Study Visits 6.5 Data Collection	-	-	Additional edits made to include additional 12 months of optional follow-up (12-36 months total)

9.1 Safety Considerations and Monitoring			

10.1 Primary aim - Safety	…over the duration of the extension trial…	…over 12 months of the extension trial…	The duration over extension trial (up to 36 months) is added as a secondary safety aim (see below)
10.1.2 Secondary aim - Safety	-	10.1.2 Secondary aim – Safety The secondary safety outcome will be reported similar to Primary safety outcome (see above), but over a longer period of time including additional FU period (i.e. for up to 36 months on the study).	Additional safety summary for for AEs over the longest available period (up to 36 months)

October 30, 2020

Location of Change	*Change from*	*Changed to*	*Comment*
2. Protocol Synopsis – Study Duration	Approximately 12-15 months (recruitment plus study procedures and follow up phone calls). The trial may be extended by up to an additional 24-27 months for those opting to continue for a second year.	Approximately 12-15 months (recruitment plus study procedures and follow up phone calls). The trial may be extended by up to an additional 36-39 months for those opting to continue for additional follow-up.	Adding an option for a fourth year on open label udenafil for those subjects interested in remaining on study drug.
4.2 Secondary Aims	Secondary Aim 5: Evaluate the safety of udenafil (87.5 mg bid) in adolescents with Fontan physiology over an additional 12 months (study months 12-36).	Secondary Aim 5: Evaluate the safety of udenafil (87.5 mg bid) in adolescents with Fontan physiology over an additional 12 months (study months 12-48).	Updated to include additional 12 months of follow-up
5.3 Rationale for the Study 6.1 Study Overview 6.4 Study Visits 6.5 Data Collection 9.1 Safety Considerations and Monitoring	-	-	Additional edits made to include additional 12 months of optional follow-up (12-48 months total) and quarterly telephone calls
6.4 Study Visits	Week 2 and Week 13 Follow-Up Visits – South Korean Sites Only		Removed references to South Korea as no South Korean study sites were activated for the FUEL OLE study
Table 1 Schedule of Events			Frequency of calls changed from monthly to quarterly; total number of calls updated
8.3 Procedures for Monitoring & Subject Adherence 9.1 Safety Considerations and Monitoring	Monthly calls	Quarterly calls	Frequency of telephone calls changed from monthly to quarterly

10.1.2 Secondary aim - Safety	The secondary safety outcome will be reported similar to Primary safety outcome (see above), but over a longer period of time including additional FU period (i.e. for up to 36 months on the study).	The secondary safety outcome will be reported similar to Primary safety outcome (see above), but over a longer period of time including additional FU period (i.e. for up to 48 months on the study).	Updated to include additional 12 months of follow-up

1. PROTOCOL SIGNATURE PAGE

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in accordance with the design and specific provisions outlined herein; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use the informed consent form approved by the NHLBI and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board or Ethics Committee responsible for this study.

I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 9.2.4 of this protocol.

I further agree that the NHLBI and/or its designee has access to any source documents from which case report form information may have been generated.

I also agree to handle all clinical supplies (including drugs, biologics, and/or devices) provided by Mezzion® and collect and handle all clinical specimens in accordance with the protocol.

The below signed confirm herewith to have read and understood this study protocol and/or amendment and appendices; furthermore, to accomplish this study in accordance to the protocol and Good Clinical Practice guidelines, as well as local regulations and regulatory authorities.

PRINTED or TYPED NAME(S)	SIGNATURE	DATE
Investigator		
Investigator		
Investigator		
Investigator		

2. Protocol Synopsis

Protocol Title	A Phase III Safety Extension Study of Udenafil in Adolescents with Single Ventricle Physiology after Fontan Palliation (FUEL Extension)
Protocol Number	PHN-Udenafil-03
US IND Number	121648
Grant Number	NHLBI U01 HL068270, HL109741, HL109781, HL109816, HL109818, HL109777, HL109778, HL109673, HL109743, HL109737, HL068270
Clinical Phase / Indication	Phase 3 Safety of udenafil in adolescents with Fontan physiology
Study Objectives	1) Determine the safety of udenafil (87.5 mg, twice daily) in an adolescent population with single ventricle congenital heart disease palliated with the Fontan procedure. 2) Evaluate the pharmacodynamic profile of udenafil over a one to three year period.
Significance	The Fontan Udenafil Exercise Longitudinal Study is planned to evaluate the efficacy and safety of udenafil over a six-month period. However, an understanding of the longer-term safety profile of udenafil is critical prior to adopting it for use in those with Fontan physiology.
Study Design	Open label extension trial of udenafil (87.5 mg twice daily).
Primary Safety Measurements	Safety will be assessed by monitoring adverse events and vital signs, clinical laboratory test results, 12-lead ECG, and physical examinations.
Other Safety Measurements	The effect of treatment on the functional health status in adolescents following a Fontan procedure. The effect of treatment on the prevalence and severity of complications, including protein-losing enteropathy (PLE), plastic bronchitis, hospitalizations, cardiac transplantation, and death in adolescents who receive udenafil following the Fontan procedure.
Efficacy Measurements	Evaluate the effect of udenafil on pharmacodynamic outcomes including exercise capacity, echocardiographic measures of ventricular function, endothelial function, and serum biomarkers, as well as measures of functional health status / quality of life. Explore the impact of udenafil on atrial and ventricular premature beats and arrhythmia burden – optional for a subset of new participants.
Sample Size	All subjects enrolled in FUEL trial, with minimum of 300 subjects
Study Duration	Approximately 12-15 months (recruitment plus study procedures and follow up phone calls). Participation in the trial may be extended up to an additional 36-39 months for those opting to continue for additional follow-up (includes 3 months of follow-up after last study dose).

Inclusion Criteria	1. Males and females with Fontan physiology who participated in the FUEL trial or, if they did not participate in FUEL, those who are 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
Exclusion Criteria	1. Height < 132 cm. 2. Weight < 40 kg. 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 three 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 mm Hg between the regions proximal and distal to the obstruction as measured by either catheterization or echocardiography. 8. Single lung physiology. 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 six months prior to enrollment. 11. Severe valvar regurgitation, ventricular outflow obstruction, or aortic arch obstruction assessed by clinical echocardiography within six months prior to enrollment. 12. Significant renal, hepatic, gastrointestinal or biliary disorders that could impair absorption, metabolism or excretion of orally administered medications. 13. Inability to complete exercise testing at baseline screening. 14. History of PDE-5 inhibitor use (with the exception of FUEL participation) within 3 months before study onset. 15. Use of any other drug to treat pulmonary hypertension within 3 months before study onset. 16. Known intolerance, including hypersensitivity or allergy history,to oral udenafil or any components of the investigational product. 17. Frequent use of medications or other substances that inhibit or induce CYP3A4. 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. 23. Unable to abstain or limit intake of grapefruit juice during the duration of the trial. 24. Refusal to provide written informed consent/assent. 25. In the opinion of the primary care physician, the subject is likely to be non-compliant with the study protocol. 26. History of clinically significant thromboembolic event, as adjudicated by study Investigators that may put the subject at increased risk of a subsequent event while participating in the study

3. Table of Contents

List of Abbreviations

AE	Adverse event
ADL	Activities of daily living
BNP	Brain-type natriuretic peptide
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
DCC	Data coordinating center
DSMB	Data and Safety Monitoring Board
EDC	Electronic data capture
FDA	Food and drug administration
ID	Identification
IND	Investigational new drug
IRB	Institutional Review Board
MedDRA	Medical dictionary for drug regulatory activities
MM	Medical monitor
MPI	Myocardial performance index
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
OLE	Open label extension
PAT	Pulse amplitude tonometry
PCQLI	Pediatric Cardiac Quality of Life Inventory
PD	Pharmacodynamic
PDE5	Phosphodiesterase type 5
PHN	Pediatric Heart Network
PI	Principal investigator
PK	Pharmacokinetic
QA	Quality assurance
QC	Quality control
RCT	Randomized clinical trial
REB	Research Ethics Board
SAE	Serious adverse event
sGC	Soluble guanylate cyclase
VO_2	Oxygen consumption

4. STUDY AIMS AND HYPOTHESES

4.1 Primary Aim

Evaluate the safety of udenafil (87.5 mg bid) in adolescents with Fontan physiology over a 12-month period.

Hypothesis: Udenafil will be safe and well tolerated over the 12-month study period.

Primary outcome: Adverse events will be collected and recorded. Adverse events will be categorized by severity and relationship to drug.

Secondary Outcome
Death, hospitalization, and heart transplantation information will be collected and evaluated.

4.2 Secondary Aim(s)

Secondary Aim 1: Evaluate the effect of udenafil on pharmacodynamic (PD) outcomes including: exercise capacity, echocardiographic measures of ventricular function, endothelial function, and biomarkers associated with heart failure over a 12-month period.

Hypothesis: PD outcomes will improve following administration of udenafil.

Primary Outcomes:

- Exercise: Change in maximal oxygen consumption from baseline to Week 52 testing measured using a standardized exercise test.
- Echo: Change in myocardial performance index as measured by pulse wave Doppler echocardiography from baseline to Week 52 testing.
- Endothelial Function: Change in log-transformed Reactive Hyperemia Index derived from the EndoPAT® device.
- Biomarkers: Change in serum BNP level from baseline to Week 52.

Secondary Outcomes:

- Exercise: Submaximal measures of exercise capacity will be collected and evaluated.
- Echo: Measure of systolic and diastolic function will be collected from a targeted echocardiogram.

Secondary Aim 2: Determine if 12 months of treatment with oral udenafil will alter functional health status in adolescents following the Fontan procedure as measured by standardized quality of life surveys.

Hypothesis: Functional health status will improve following administration of udenafil.

Primary Outcome: Change in functional health status from baseline to Week 52 as measured by the full scale PedsQL.

Secondary Outcomes:
12-month change in:

- Peds QL physical functioning Score
- Peds QL psychosocial functioning Score
- Peds QL cardiac-specific module quality of life score
- Pediatric Cardiac Quality of Life Inventory (PCQLI) Score

Secondary Aim 3: Establish a collection of genetic material to identify genetic determinants of response to udenafil after the Fontan procedure in persons with single-ventricle lesions, and for unspecified future studies. **[This aim will only apply to those who did not provide a sample for the FUEL study].**

Secondary Aim 4: Determine the prevalence and severity of complications, including protein-losing enteropathy (PLE), plastic bronchitis, hospitalizations, cardiac transplantation and death, in adolescents who receive udenafil following the Fontan operation.

Secondary Aim 5: Evaluate the safety of udenafil (87.5 mg) bid in adolescents with Fontan physiology over an additional follow-up period (study months 12-36). [This aim is an opt-in aim for those who choose to remain on drug for up to an additional 36 months].

Primary outcome: Adverse events will be collected and recorded. Adverse events will be categorized by severity and relationship to drug.

Secondary Outcome
Death, hospitalization, and heart transplantation information will be collected and evaluated.

Secondary Aim 6: Assess arrhythmia burden before and after taking study drug at baseline visit (for non-FUEL subjects only; patient participation is optional)
Outcome: Occurance, duration and speed of atrial or ventricular arrhythmias, as well as number of premature beats will be collected and evaluated.

5. BACKGROUND INFORMATION

5.1 The circulation after the Fontan procedure and potential role for PDE5 inhibitors

The Fontan operation is a palliative procedure for children born with functional single ventricle congenital heart disease[1,2]. This operation, which creates a total cavopulmonary connection, separates the systemic and pulmonary circuits and eliminates both hypoxemia and ventricular volume overload. However, following the Fontan operation there is no ventricular pump to propel blood into the pulmonary arteries. Instead blood returns to the lungs via passive flow from the systemic veins. This results in a circulation characterized by elevated central venous pressure, abnormal pulmonary vascular resistance, and a chronically low cardiac output. Over time, these inherent characteristics of Fontan physiology result in a predictable, persistent deterioration of cardiovascular efficiency, as marked by a progressive decline in exercise performance that begins after puberty[3-6]. This decline in exercise capacity correlates with an increase in symptoms from cardiovascular dysfunction and may result in the need for hospitalization, escalation of heart failure management, or transplant[7-10]. The threshold at which significant impairment is reached is variable among patients, but typically occurs sometime in the third decade of life.

A medication that addresses the central deficiencies of Fontan physiology may help to allow for a longer duration of efficient function of this circulation, and may therefore increase the duration and quality of transplant-free survival. Short-term pilot data evaluating the use of sildenafil, a PDE5 inhibitor, suggest a potential role for this class of medication for patients with the Fontan circulation[11, 12].

5.2 PDE5 inhibitors in patients with Fontan physiology

PDE5 inhibitors are a unique class of medication that have demonstrated utility in reducing

pulmonary vascular resistance and improving ventricular performance in patients with pulmonary hypertension and myocardial dysfunction[13-17]. These characteristics make them potentially attractive as a therapy for the Fontan population in which cardiac output, and thus exercise, are limited by the absence of a sub-pulmonary ventricle[18]. In limited short-term studies in children and adolescents with Fontan physiology, treatment with sildenafil, a three-times daily PDE5 inhibitor, has been safe and has shown a modest benefit in exercise performance and ventricular function[11, 19].

Given this background the FUEL trial, a large-scale randomized clinical trial (RCT), was designed and is expected to begin in the second quarter of 2016. The primary aim of the RCT is to evaluate the impact of udenafil (a twice-daily PDE5 inhibitor new to the United States) on exercise capacity in adolescents with Fontan physiology. Regardless of the outcome of the efficacy trial, longer-term safety data is imperative prior to wide-scale usage of this medication.

5.3 Rationale for the Study

While the six-month treatment with long-term utility of udenafil in adolescents with Fontan physiology is being evaluated in the FUEL trial, the novel nature of this drug in this specific population calls for a more thorough investigation of longer-term safety. Indeed, the Food and Drug Administration requires additional safety data before an indication for this drug in this population will be issued. With that need in mind, we propose a 12-month open label FUEL Extension Study (with an option to extend for up to an additional 36 months) to evaluate the safety of longer-term use of udenafil in adolescents with Fontan physiology.

We will collect and record adverse events throughout the duration of the extension trial with specific attention on the composite endpoint of death, heart failure associated hospitalization, and heart transplantation. We will also collect PD data to mirror that which is being collected in the FUEL trial to evaluate whether any potential PD improvements are maintained over a longer period of time. If udenafil is demonstrated to provide a sustained improvement in PD parameters, this would have important implications for guiding duration of therapy.

5.4 Rationale for Study Outcomes

Safety Data: The short-term safety data of PDE5 inhibitors in those with Fontan physiology has been established by a number of previous studies including the recently concluded Fontan Udenafil Phase I/II Trial, undertaken by a subset of PHN core sites. These data suggest that PDE5 inhibitors in general, and udenafil specifically, are safe in this population with side effects limited to those known to be associated with PDE5 inhibitor use. In the Fontan Udenafil Trial there were no serious adverse events associated with udenafil.

Pharmacodynamics: The primary and secondary PD aims of the FUEL trial are designed to evaluate the efficacy of udenafil on a number of important PD parameters. These include measures of exercise capacity, ventricular function (as measured by echocardiography), endothelial function, and biomarkers associated with heart failure. In the FUEL extension trial we will evaluate these parameters at study entrance (using end-of-study measures for those who participated in FUEL) and again at end-of-study. The durability of any improvement noted in FUEL is important, as it may help to inform clinical decisions regarding long-term therapy.

Biorepository: The response to udenafil may also be influenced by variants influencing the vascular response to udenafil. Variants in the endothelial nitric oxide synthase gene have been reported to influence the response to sildenafil in patients with erectile dysfunction, although this has not been studied for udenafil[20]. Variation in genes that regulate the vascular, inotropic and chronotropic response to exercise may influence the exercise capacity of patients after the

Fontan procedure as well as the response to udenafil. DNA will be stored to perform future genotyping studies to analyze the genetic contribution to the response to udenafil.

Functional Health Status: In the PHN Fontan Cross-Sectional Study, physical and psychosocial functional statuses were significantly reduced across almost all domains[21, 22]. It is clear that overall functional status is significantly reduced in this population compared to a healthy control population[23]. Given these findings, a highly desirable goal of any therapy to improve or maintain function in the population with the Fontan procedure would be maintenance or improvement in overall health status. However, in the PHN study, none of the evaluated measures of exercise performance including percent of predicted maximal VO_2 significantly correlated with measures of physical functioning or psychosocial domains[22]. Given these findings, even a positive effect of udenafil therapy on aerobic capacity may not necessarily result in improved functional status.

Under these circumstances, any change in functional status over time that is associated with udenafil therapy would be an extremely important outcome.

6. STUDY / TRIAL DESIGN

6.1 Overview

This study is a 12-month (52 week) safety extension study, with an option for up to an additional 36 months, to supplement the FUEL Phase III clinical trial to provide a more robust safety and side-effect profile of the use of udenafil in adolescents with Fontan physiology. We will attempt to recruit all participants who completed the FUEL trial, a potential of approximately 400 subjects, and will supplement, if needed, with additional adolescents with Fontan physiology until the minimum of 300 total subjects have been enrolled.

Figure 1 Trial Schema

6.2 Study Design

This will be an open-label extension study. All enrolled subjects will be provided with udenafil, at a dose of 87.5 mg bid, for the duration of the study. Importantly, once the results of FUEL are known, these will be presented to the DSMB which will then provide a recommendation as to whether the FUEL extension trial should continue. If a total lack of efficacy is determined, the extension trial may be discontinued.

6.3 Study Measures

6.3.1 Measures of Primary Aim (Safety)

All adverse events will be collected and recorded for the duration of the trial.

6.3.2 Measures of Secondary Aims (Pharmacodynamics)

Primary Outcomes:

- Exercise: Change in maximal oxygen consumption from FUEL extension baseline (will be end-of-study testing for FUEL participants) to testing at 12 months measured using a standardized exercise test.
- Echo: Change in myocardial performance index as measured by pulse wave Doppler echocardiography from baseline to testing at 12 months.
- Endothelial Function: Change in log-transformed Reactive Hyperemia Index derived from the EndoPAT® device.
- Functional Health Status: Change in full scale Peds QL
- Biomarkers: Change in serum BNP level from baseline to testing at 12 months.

Secondary Outcomes:

- Exercise: Submaximal measures of exercise capacity will be collected and evaluated.
- Echo: Measure of systolic and diastolic function will be collected from a targeted echocardiogram.
- Functional Health Status: Change in Peds QL physical functioning score, psychosocial functioning score, and cardiac-specific quality of life score. Change in Pediatric Cardiac Quality of Life Inventory (PCQLI) score.
- Arrhythmia Burden (limited to non-FUEL subjects; participation is optional) will be assessed at 2 time points: pre-study drug and post-study drug (both during the baseline visit): Number of premature atrial or ventricular beats (2 outcomes) as a percentage of total beats over the course of heart-rhythm monitoring from pre-study drug measurements compared to taking study drug. Occurrence, duration and speed of atrial or ventricular

arrhythmias (2 outcomes), and comparison between the two time points.

6.3.3 Covariate Measures

We will attempt to identify possible associations between a variety of clinical factors and both safety and PD outcomes. Examples of clinical factors include:

- Age
- Gender
- Race/ethnicity
- Height/weight
- Ventricular morphology
- Resting oxygen saturation
- Baseline pharmacodynamic test results
- Current medication use

6.4 Study Visits

Baseline Visit – For those subjects who WERE participants in the FUEL Trial:

1. Baseline screen
   Prior to study enrollment, patients will be screened to ensure that all inclusion criteria are met and none of the exclusion criteria are present. The safety labs for FUEL will be accepted as meeting the inclusion criteria for FUEL extension. Pregnancy testing for OLE will be done at every in-person visit via a urine or serum pregnancy test for female participants. If the pregnancy test is positive all further testing will be stopped, the patient will not be enrolled into the trial and the result will be conveyed to the subject and/or guardians by the site-principal investigator in accordance with local IRB procedures.

2. Informed consent
   Informed consent and assent for FUEL Extension will be obtained (if not obtained prior) as per local IRB/REB requirements during the end-of-study visit for FUEL.

3. Baseline PD testing
   End-of-study pharmacodynamic testing for FUEL will serve as baseline testing for FUEL Extension.

4. Quality of life surveys
   End-of study quality of life survey results (Peds QL, Peds QL cardiac specific module, PCQLI), HAES for FUEL will serve as baseline testing for FUEL Extension

5. Initiation of study drug (See Table 2)
   Subjects will return to their study center in the shortest period of time deemed practical, following FUEL study completion, for study drug initiation under direct observation. During this visit, a resting blood pressure and heart rate will be obtained just prior to dosing. One dose of the study medication will be administered to the subject. At approximately 2 hours (+/- 30 minutes) post dosing, an additional resting heart rate and blood pressure will be measured and the subject will asked to perform a self-limited 6-minute walk. A repeat heart rate and blood pressure will be measured immediately following the 6 minute walk and a blood sample will be obtained for determination of udenafil and metabolite concentration. At approximately 2 hours (+/- 30 minutes) following the 6-minute walk, a final resting heart rate and blood pressure will be obtained, adverse events will be recorded, and the subject will be dispensed their initial supply of study medication. The subject will be instructed to take the medication twice a day and to bring back the medication bottle for their next in-person visit.

The subject will then be discharged from the clinic. Importantly, if the subject has a drop in systolic blood pressure > 20 mmHG from the pre- to post-6 minute walk measurement, or if the systolic blood pressure drops below the 5th percentile for age (calculated by 2 x age + 65), they will be excluded from receiving any further study drug. These subjects will be followed for 90 days per the FUEL protocol for adverse event monitoring.

Baseline Visit - For those subjects who WERE NOT participants in the FUEL Trial:
The baseline visit consists of two parts, baseline testing and study drug initiation. These parts may be combined into a single day, or split into two days so long as the duration of time between the visits is no more than 7 days.

1. Baseline screen
   Prior to study enrollment, patients will be screened to ensure that all inclusion criteria are met and none of the exclusion criteria are present.

2. Informed consent
   On the day of the first study visit, informed consent and assent will be obtained (if not obtained prior) as per local IRB requirements.

3. Baseline PD testing and safety labs
   The EndoPAT® vascular assessment will be completed as the first PD test following consent. This must be performed in a fasting (from midnight until after the test), non-caffeinated state. After the vascular assessment, subjects will have a targeted echocardiogram to assess ventricular function. A short break will be given, either after the vascular assessment or after the echocardiogram, and a light snack will be provided. Safety labs will be performed following the vascular assessment, echocardiogram, and break. These will include collection of blood to evaluate serum creatinine and liver enzyme (aspartate transaminase and alanine transaminase) levels for all participants, and a urine or serum pregnancy test for female participants. If the pregnancy test is positive all further testing will be stopped, the patient will not be enrolled into the trial and the result will be conveyed to the subject and/or guardians by the site-principal investigator in accordance with local IRB procedures. After the safety labs, an exercise test will be administered using a braked cycle ergometer following a ramp protocol previously published in the PHN Fontan Cross-Sectional Study[3]. As with the FUEL study, subjects who fail to achieve a maximal effort on a baseline exercise test will be offered an opportunity to repeat the test within a 2 week time window. After exercise testing, subjects will have completed the baseline testing.

4. Quality of life surveys
   The Peds QL, cardiac specific Peds QL, HAES and PCQLI will be administered during the baseline testing visit.

5. Initiation of study drug (see Table 2)
   Study drug initiation will occur under direct observation. A resting blood pressure and heart rate will be obtained just prior to dosing. One dose of the study medication will be administered to the subject. At approximately 2 hours (+/- 30 minutes) post dosing, an additional resting heart rate and blood pressure will be measured and the subject will asked to perform a self-limited 6-minute walk. A repeat heart rate and blood pressure will be measured immediately following the 6 minute walk and a blood sample will be obtained for determination of udenafil and metabolite concentration. At approximately 2 hours (+/- 30 minutes) following the 6-minute walk, a final resting heart rate and blood pressure will be obtained, adverse events will be recorded, and the subject will be dispensed their initial

supply of study medication. The subject will be instructed to take the medication twice a day and to bring back the medication bottle for their next in-person visit. The subject will then be discharged from the clinic. Importantly, if the subject has a drop in systolic blood pressure > 20 mmHG from the pre- to post-6 minute walk measurement, or if the systolic blood pressure drops below the 5th percentile for age (calculated by 2 x age + 65), they will be excluded from receiving any further study drug. These subjects will be followed for 30 days for adverse event monitoring.

6. Baseline Visit Day 1 of 2: Heart Rhythm Monitoring pre-study drug dose
   At study initiation, a subset of FUEL Extension subjects who were not in the FUEL Trial will have the opportunity to enroll in a heart rhythm-monitoring study. Heart rhythm monitoring will include a 3 to 7-day baseline monitor followed by a 3-day steady state monitor. Enrollment in the heart rhythm-monitoring arm will require that subjects split the baseline visit such that baseline testing is performed 3 to 7 days prior to drug initiation. At the conclusion of baseline testing on day 1 of 2, the heart monitor will be placed on the subject. The device will be worn for 3 to 7 days and removed when the patient returns for study drug initiation (baseline visit day 2 of 2). The device, identified only by the subject's study identification number, will then be sent to the vendor for generation of a report..

7. Baseline Visit Day 2 of 2: Heart Rhythm Monitoring after study drug dose
   For those who opted to participate in the heart rhythm-monitoring subset and completed a minimum of three days of baseline monitoring (day 1 of 2), a second device will be placed on the subject at the conclusion of the second day of the baseline visit (day 2 of 2) after study drug initiation. The device will be worn for 72 hours after which the subject will be instructed to mail the device, identified only by their study subject number, to the vendor for download and generation of a report.
   The report will be returned to the enrolling site and any change in the frequency of premature beats or arrhythmias will be shared with the DSMB as summary data in accordance with standard reporting. A change in arrhythmias felt to rise to the level of a serious adverse event will be reported to the Medical Monitor in accordance with serious adverse event reporting (**section 9.3**).

Week 52 Testing

At Week 52, the subject will undergo testing for primary and secondary efficacy endpoints. Testing for this visit will include an exercise test, an echocardiogram, EndoPAT®, BNP, quality of life questionnaires and safety labs. To minimize any potential effect of the timing of administration of the study drug on testing outcomes, the time of the study drug dosing on the visit day will be standardized. Additionally, if a subject is unable to achieve a maximal effort on exercise testing, they will be offered the opportunity to repeat the EST within two weeks (14 days) of the first test. During this time period, the subject should remain on udenafil. If they achieve a maximal effort on this second study, the results of the second study will be used in the analyses.

At Week 52, vital signs (Resting Blood Pressure/Heart rate) will be obtained; assessment of adverse events, concomitant medications, drug accountability and a blood sample will be drawn for determination of udenafil and metabolite concentration immediately following the exercise test. For female subjects, serum or urine pregnancy test will be administered.

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Telephone Contact (Between Baseline and Week 52)

Study coordinators will call each subject the day after drug initiation to ensure the study drug is well tolerated. Subjects will be called at weeks 1, 2, 3, 4, 8, 13, 17, 21, 30, 34, 39, 43, 47 to monitor

adherence, to collect medical history data, and record adverse events through 52 weeks. They will also be called 30 and 90 days after Week 52 to record adverse events. Subjects will be encouraged to notify the study coordinator between scheduled contact dates with any new onset symptoms or complications.

Post-Week 52 Follow-up

Option 1: discontinuation of study drug
If a participant chooses to discontinue study drug after Week 52, a study coordinator will call the subject at 30 (week 56) and 90 days (week 64) to record any additional adverse events possibly or probably related to study drug that may have occurred in the 90 days following completion of the study protocol.

Option 2: continuation of study drug for up to 36 additional months
Following the Week 52 visit, participants will have the option of continuing on in FUEL-Extension for up to 36 months. During this time, safety data will be collected. Participants will be contacted by the study coordinator on a quarterly basis to monitor and record adverse events. Once study drug has been discontinued (maximum of 36 months following Week 52), subjects will be contacted at 30 days and 90 days following cessation of study drug to monitor for additional adverse events after discontinuation of drug.

For participants who have completed the 24-month extension and have stopped taking study drug for any period of time perior to re-consenting to version 6, the only testing needed prior to re-initiating study drug is a pregnancy test for female participants.

Table 1. Schedule of Events

Visit Number	1	1	TC1	TC 2-15	2	TC 16-17	TC 16 - 28	
Subject Status	New subject (no FUEL)	Former FUEL subject				Post week 52 Option 1	Post Week 52 Option 2	
Time point	Screening/ Baseline Day 0	Screening/ Baseline Day 0	Day 1	Weeks 1, 2, 3, 4, 8, 13, 17, 21, 30, 34, 39, 43, 47	Week 52	Day 30, 90 post-study (Weeks 56 and 64)	Quarterly	Day 30, 90 post-drug discontinue
Visit Window(s)				± 3 days	± 10 days	± 10 days		
Type of Visit(s)	In-Person	In-Person	Call	Calls*	In-Person	Calls	Calls	Calls
Informed Consent/Assent	X	X						
Subject ID# assigned	X							
Inclusion/Exclusion Criteria	X							
Physical Measurements	X							
Medical history	X							
Demographics/expanded demo	X							
Prior/Concomitant Meds	X			X	X			
EndoPAT®	X				X			
Serum or urine pregnancy test	X	X			X			
Clinical Laboratory tests (creatinine, ALT, AST)	X				X			
Biomarker (BNP) sample	X				X			
Genetic repository sample (optional)	X							
Heart Monitor (optional)	X							
Echocardiogram	X				X			
Exercise test (EST)	X[a]				X[a]			
Dispense Open Label Udenafil[b]	X	X						
Resting BP and HR[c]	X	X			X			
Administer first dose of study drug[c]	X	X						
Peds QL generic and cardiac modules; PCQLI; HAES	X				X			
Drug Accountability[b]	X				X			
Pregnancy counseling (if appl)	X	X		X				
Adverse events assessment		X	X	X	X	X	X	X
Morisky Scale (MMAS)				X				
Schedule/Confirm next visit	X	X	X	X	X			

[a] If failed 1st exercise test, exercise testing can be repeated w/in 14 days. Pregnancy testing must also be repeated.
[b] For detailed Drug Accountability procedures, consult the Manual of Operations (MOO)
[c] For specific timing of procedures, see Additional Procedures and Measurements in Table 2

Table 2. Initiation of Study Drug

	Time from administering first dose of study medication			
Procedure	**<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		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

6.5 Data Collection

1. Demographic information

   The following demographic data will be collected: age, gender, race, ethnicity, cardiac anatomy, date of Fontan, presence of a fenestration, degree of atrioventricular valve regurgitation, grade of ventricular function, concomitant medications, and significant co-morbidities.

2. Safety data

   Adverse events will be reviewed with each subject at each study visit and during telephone encounters. These events will be recorded and graded by severity and relationship to study drug based on established criteria. Two additional telephone encounters will take place 30 days and 90 days following cessation of study drug [either at Week 52 or up to Week 208 if the subject opts to continue study drug] to assess for any adverse events possibly or probably related to study drug in the period following the completion of study procedures.

3. Exercise stress test

   Data from the braked cycle ergometry exercise stress tests will be collected according to protocol established in the PHN Fontan Cross-Sectional Study[3].

4. Assessment of ventricular performance

   Each study echocardiogram will be stored in a de-identified manner and sent to a core laboratory, which will perform the data analysis and submit the measurements to the PHN Data Coordinating Center (DCC).

5. Vascular function testing

   De-identified data from EndoPAT® testing will be collected according to a standardized protocol. These data will be sent to a vascular core lab, which will perform the analysis and submit the measurements to the PHN DCC.

6. Biomarkers
   Serum for measurement of BNP level will be sent to a core clinical lab. Results will be sent directly to the PHN DCC.

7. Quality of life survey
   Results of the Quality of life surveys will be submitted to the PHN DCC.

8. Samples for the biorepository
   Samples collected for the biorepository will be shipped directly to the biorepository for future analysis.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Subject Inclusion Criteria

1. Males and females with Fontan physiology who participated in the FUEL trial or, if they did not participate in FUEL, those who are 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 or Spanish
4. Current anti-platelet or anticoagulant therapy

7.2 Subject Exclusion Criteria

1. Height < 132 cm.
2. Weight < 40 kg.
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 three 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 mm Hg between the regions proximal and distal to the obstruction as measured by either catheterization or echocardiography.
8. Single lung physiology.
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 six months prior to enrollment.
11. Severe valvar regurgitation, ventricular outflow obstruction, or aortic arch obstruction assessed by clinical echocardiography within six months prior to enrollment.
12. Significant renal, hepatic, gastrointestinal or biliary disorders that could impair absorption, metabolism or excretion of orally administered medications.
13. Inability to complete exercise testing at baseline screening.
14. History of PDE-5 inhibitor use (with the exception of FUEL participation) within 3 months before study onset.
15. Use of any other drug to treat pulmonary hypertension within 3 months before study onset.
16. Known intolerance, including hypersensitivity or allergy history,to oral udenafil or any components of the investigational product.
17. Frequent use of medications or other substances that inhibit or induce CYP3A4.
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.
23. Unable to abstain or limit intake of grapefruit juice during the duration of the trial.
24. Refusal to provide written informed consent/assent.
25. In the opinion of the primary care physician, the subject is likely to be non-compliant with the study protocol.
26. History of clinically significant thromboembolic event, as adjudicated by study Investigators that may put the subject at increased risk of a subsequent event while participating in the study.

7.3 Recruitment/Enrollment Procedures

All subjects enrolled in the FUEL Trial will be offered participation in the FUEL Extension Trial. This number is anticipated to be approximately 400 subjects. If recruitment from the FUEL subjects is less than 300, additional subjects will be identified through the review of clinical data records at each participating PHN and auxiliary site. Those who are interested will be enrolled and consented at the first study visit by the study coordinator from each participating site. We plan to continue to screen and identify potential subjects until enrollment is completed. If consent is obtained for study participation but a subject is excluded on the basis of safety labs or a pregnancy test (Section 5.2), an additional subject will be recruited to replace the excluded subject.

7.4 Indications for Discontinuation of Study Drug

Study drug may be discontinued temporarily or permanently, but subjects should remain in the trial and complete all study data collection and follow-up measures, including exercise performance testing. Study drug may be discontinued for the following reasons:

- An adverse experience including failure to tolerate study medication that, in the judgment of the investigator or primary physician requires drug discontinuation.
- Voluntary discontinuation of study drug by subject.

When possible, the subject will 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 will be recorded.

7.5 Subject Withdrawal from Study

The “Week 52” testing will be obtained whenever possible on subjects who withdraw early. The reason for withdrawal will be documented for all subjects withdrawn from the study. A subject may be withdrawn from trial participation for the following reasons:

- Subject (or legal guardian) declines 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 is in the subject’s best interest.

If the subject refuses to continue with the study visits, every attempt will be made to continue contact by telephone, written communication, or record review to determine if outcome events (death, hospitalizations and major complications) have occurred, unless the subject specifically refuses such follow-up. If the withdrawing subject is 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 submit a written refusal.

8. TREATMENTS TO BE ADMINISTERED

8.1 Description of Study Treatments

All enrolled subjects will receive udenafil at a dose of 87.5 mg twice daily for the duration of the study.

8.2 Concomitant Medications

Subjects will be treated with other medications at the discretion of their physicians. At study visits, current medications will be recorded on the study forms. If a subject begins open-label use of any other PDE-5 inhibitor at any time during the study, withdrawal from study drug is 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, nefazodone, ketoconazole, posaconazole, and voriconazole.
- 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 should be avoided:
  - Boceprevir
  - PDE-5 inhibitors other than udenafil
  - Telaprevir
  - Organic nitrates including isosorbide dinitrate, isosorbide mononitrate and nitroglycerin
  - Soluble guanylate cyclase (sGC) stimulators

8.3 Procedures for Monitoring Subject Adherence

Study drug adherence will be assessed at each scheduled study contact by the study coordinator. Additionally, adherence will be calculated bi-monthly by comparing the expected versus actual consumption of study drug tablets. The study coordinator will remind the subject to return study drug bottles to the site during each call contact. Each subject will receive via traceable courier a resupply of study medication. Subjects will have the option to return all remaining study drug from previous supply to the site using a pre-paid envelope from a service provider with the capability to track the shipment (e.g. FedEx or UPS). The study coordinator or pharmacist will measure and record the number of remaining tablets. Once the pill count is complete, the pharmacy may then destroy the returned study medication according to standard operating procedure.

The study coordinator or pharmacist will measure and record the number of remaining tablets, and a study drug supply will be dispensed. Once the pill count is complete and the study drug has been monitored, the pharmacy may then destroy the returned study medication according to standard operating procedure.

Self-report of study drug compliance will be assessed with administration of the Morisky scale[24]. The Morisky scale is a questionnaire used to predict adherence to medication therapies. The scale will be administered during each quarterly contact call.

8.4 Study Completion

When an individual subject completes the study, the subject's primary cardiologist will be notified, and the study drug will be stopped; there is no need to wean subjects off of the study drugs. The decision of whether to continue the use of an off label PDE-5 inhibitor for individual subjects will be decided by the subjects and their primary cardiologist, and will be at the subject's expense or that of their third-party payer. Udenafil may also be available to study participants after the conclusion of the study through the manufacturer.

9. SAFETY ASSESSMENTS

9.1 Safety Considerations and Monitoring

The site study coordinators will contact each subject the day after the baseline visit, then weekly for four weeks and monthly until 52 weeks (12 months), and then at 30 and 90 days from the week 52 visit. If the subject is continuing into the extension of up to an additional 36 months then the site study coordinators will contact each subject quarterly until the subject discontinues study drug. At withdrawal or discontinuation, site study coordinators will contact each subject at 30 and 90 days from withdrawal or discontinuation to record adverse events.

9.2. Recording and Reporting Adverse Events

A major component of safety monitoring is ascertainment and reporting of AEs, including adverse drug reactions. The approach to these activities for this study is summarized in the sections that follow.

9.2.1 Definitions of Adverse Event, Suspected Adverse Reaction and Adverse Reaction

The FDA Final Rule on IND Safety Reporting Requirements provides the following definitions:

- *Adverse event*: any untoward (e.g. unfavorable, negative, or harmful) medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug related. An event can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the product.
- *Suspected Adverse Reaction*: any AE for which there is a reasonable possibility that the drug caused the event, meaning the event is possibly, probably related to the study drug.
- *Adverse Reaction*: an AE for which there is a greater degree of certainty regarding causality; meaning the event is probably or definitely related to the study drug. Adverse reactions are a subset of Suspected Adverse Reactions.

9.2.2 Classification of Adverse Events

Monitoring AEs requires that they be classified as to seriousness, expectedness, and potential relationship to the study drugs, all of which drive the reporting process.

a. Seriousness

An SAE is one that:

- Results in death,
- Is life-threatening (the subject was, in the view of the Principal Investigator, in immediate danger of death from the event as it occurred),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Is a congenital anomaly/birth defect in the offspring of a participant, or
- Is an Important Medical Event that may jeopardize the subject or may require

medical/surgical intervention to prevent one of the serious adverse event outcomes.

The Common Terminology Criteria for Adverse Events (CTCAE) and MedDRA (http://ctep.cancer.gov) provide a grading system and terminology that is used to identify and categorize the severity of adverse events, as follows:

Grade	Severity	Definition
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 (ADL).
3	Severe	Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Life-threatenin	Life-threatening consequences; urgent intervention indicated.
5	Death	Death related to AE

An SAE, as defined above, encompasses CTCAE grades 4 and 5, and any Grade 3 event that requires or prolongs hospitalization, or that substantially disrupts the ability of the subject to conduct normal life functions.

b. Expectedness

The purpose of reporting is to provide new, important information on serious reactions or events previously unobserved or undocumented. Therefore, all AEs will be evaluated as to whether their occurrence was unexpected, using the following definitions:

- *Unexpected*: An unexpected AE or adverse reaction is one for which the nature or severity is not consistent with information in the protocol, consent form, or product brochure. An AE or adverse reaction also may be categorized as unexpected if the event has not previously been observed at the same specificity and/or severity. There may be unexpected adverse events in female participants in whom this class of medication has not been extensively studied.
- *Expected*: An event is considered expected if it is known to be associated with the study drug(s) and/or the disease state. According to the product brochure (attached; English translation from Korean) and for this protocol, expected events include:
  - *Spontaneous penile erection*
  - *Facial flushing* (> 10%)*Headache (1-10%)*
  - *Eye redness (1-10%)*
  - *Dyspepsia (1-10%)*
  - *Nasal congestion (1-10%)*

c. Causality

Causality assessment is required to determine which events require expedited reporting. The following criteria will be used to determine causality:

- *Not Related*: The event is clearly related to other factors, such as the subject's clinical state, or non-study drugs or interventions.
- *Possibly Related*: The event follows 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 follows a reasonable temporal sequence from the time of drug administration, and cannot be reasonably explained by other factors such as the

subject's clinical state, or non-study drugs or interventions.

9.2.3 Identification of and Data Collection Procedures for Adverse Events

AEs will be identified when they are reported to the clinical center or during scheduled study visits by study coordinators and investigators. AEs will be assessed using self-report, physical examination data, and medical record review.

9.2.4 Reporting Procedures

Fatal or life-threatening AEs are to be reported to the data coordinating center (DCC) within 24 hours of first knowledge of the event. Those that are unexpected and considered possibly, probably, or definitely related to the study drug (udenafil) will be reported by the DCC to the FDA, the DSMB Chair, the medical monitor (MM), the National Heart, Lung, and Blood Institute (NHLBI), and all study Investigators as soon as possible, but no later than 7 calendar days after first knowledge of the event, followed by a complete report within 15 calendar days. All other fatal or life threatening events that are unrelated to study drug (udenafil) will be reported semiannually to the DSMB and the NHLBI, and annually to the FDA.

Seriousness	Reporting Timeframe	Notification Timeframe
Fatal or life threatening	Within 24 hour of learning of the event	Within 7 calendar days after report
Serious, but not fatal or life threatening, and pregnancy	Within 24 hours of learning of the event	Within 15 calendar days after report
All other	Within 7 calendar days of learning of the event	Within 15 calendar days after report

All other *SAEs (i.e., non-fatal or not life-threatening)* that are unexpected and considered possibly, probably, or definitely related to the study drug will be reported to the DCC within 24 hours of learning of the event. The DCC will report the event to the FDA, NHLBI, DSMB and all study Investigators within 15 calendar days after first knowledge of the event.

All other *AEs* not meeting the criteria for expedited reporting will be reported to the DCC within 7 calendar days of first knowledge of the event. The DCC will report these AEs quarterly to NHLBI and annually to the FDA.

9.2.5 Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multi-Center Clinical Trials

The site Investigator or designee is responsible for reporting all serious adverse events to the local IRB in accordance with local policies and procedures.

A Data and Safety Monitoring Board (DSMB) Summary Report will be prepared within 30 days of each meeting and distributed by NHLBI staff to each Principal Investigator and Study Coordinator. The Summary Report will include information that the DSMB met, they reviewed the study for safety, and which recommendations were made related to the study. The report is to be forwarded to the local IRB.

9.2.6 Follow-up of Subjects after Adverse Events

For AEs with a causal relationship to the study product, follow-up by the Investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator.

9.3 Safety Monitoring

The Data and Safety Monitoring Plan for this trial will follow standard PHN monitoring principles. Oversight of data and safety is provided by the PHN DSMB, appointed by NHLBI. The DSMB meets at least twice a year to review data on AEs, adverse reactions, suspected adverse reactions, patient-reported outcomes, data quality, and study recruitment at regular intervals, and makes recommendations about study conduct to the Director of the Division of Cardiovascular Sciences, NHLBI.

The DSMB and NHLBI are assisted by a MM in reviewing serious adverse events in PHN studies. The PHN MM is the NHLBI's designee for determining causality and expectedness of all SAEs.

10. STATISTICS

10.1 Primary Aim - Safety

The primary safety outcome is adverse events. The adverse events will be reported by seriousness, severity and relationship with the study drug. Additionally, the number of subjects experiencing a composite outcome of death, heart failure associated hospitalization, or heart transplant will be reported. The overall assessment of safety will be made on the basis of all available adverse events and safety outcome data over the duration of the 12 months extension trial and an additional 90 days following completion of the study protocol.

10.1.2 Secondary aim – Safety

The secondary safety outcome will be reported similar to Primary safety outcome (see above), but over a longer period of time including additional FU period (i.e. for up to 48 months on the study).

10.2 Secondary Aims - Efficacy

Primary outcomes for secondary aims

Changes in myocardial performance index as measured by pulse wave Doppler echocardiography over 12 months of the follow-up from the extension trial baseline till end-of-study testing will be calculated. Student's t-test for location will be used to determine if mean change is different from zero. A similar approach will be applied to maximal oxygen consumption determined by exercise testing for subjects who reached maximal effort at both time points.

Similarly, changes in serum BNP level and pulse amplitude tonometry ratio derived from the EndoPAT device over 12 months of the follow-up from the extension trial baseline till end-of-study testing will be calculated. The Wilcoxon signed rank test for location will be used to determine if median change of each of these outcomes is different from zero.

For secondary efficacy aim focused on maximal oxygen consumption, estimated power to test potential secondary hypothesis is calculated conditional on the target sample size of 250 subjects (a conservative estimate for number of subjects with paired max effort exercise measurements). The estimate below is provided strictly as an illustration, since there will be no formal hypotheses testing for secondary outcomes.

Assuming 250 subjects with paired max effort exercise measurements, baseline mean value of maximal VO2: 28.0±6.25 ml/kg/min and correlation between baseline and 12-month measurements for maximal VO2: 1/3 (based on historical data; a conservative assumption),

we'll have 85% power to detect change of 1.4 ml/kg/min (or 0.2 of standard deviation) with type 1 error of 0.05.

Secondary outcomes for secondary aims

Secondary outcomes include submaximal measures of exercise capacity (based on exercise testing), measures of systolic and diastolic function (based on echocardiograms), and results of quality of life surveys measured at baseline and 12-month follow-up visit. Descriptive statistics will be provided for each outcome at both time points. Mean change values of the outcomes will be assessed by a paired t-test.

Missing data

Since the main goal of the follow-up study is to assess safety of the patients, imputation of missing data is not planned.

10.3 Interim analyses

No formal stopping rules for safety or efficacy are planned. However, the trial data will be reviewed on a periodic basis, at least twice per year, by the DSMB. The DSMB report will include information on safety, data quality and data completeness, overall and by center. The DSMB has the jurisdiction to recommend stopping of the trial early due to safety concerns at any time. The DSMB can recommend stopping the trial after reviewing the results of the FUEL trial if the results of FUEL suggest that continuing with FUEL extension is not necessary.

10.4 Potential Biases

Enrollment to the open label extension trial (OLE) will have two sources: rollover subjects who were previously enrolled in one of the FUEL arms (udenafil, placebo) and new subjects who didn't participate in FUEL. Since inclusion/exclusion criteria are identical for the FUEL and OLE, we don't expect differences between the rollover and new subjects.

OLE subjects will not include FUEL subjects who dropped-out or didn't consent to OLE, creating the theoretical potential for one arm of FUEL (placebo or study drug) to be over-represented in OLE. Incidence of AEs and key patient characteristics of FUEL subjects not participating in OLE will be compared by treatment arm to assess potential bias.

11. DATA MANAGEMENT

A customized data management system will be developed for the study using the DCC's secure web-based e-Clinical Operating System (eCOS). This system integrates all aspects of study data collection including: subject screening and enrollment data; real time accrual reporting; tracking of subject study appointments for follow-up; all study follow-up data collection; censoring/loss to follow-up data; and monitoring timeliness and quality of data collection.

11.1 Data Entry

The eCOS system allows direct data entry from multiple study sites via a secure web-based application. Data are entered by subject study identification number; names will not be linked with subject data in the database. Study sites will maintain local records in secure areas linking the subject name with the identification number assigned for the study. Study sites will have full access to their own data in eCOS and be able to view these data remotely. Study staff will not be able to view subject-level data associated with other sites.

11.2 Data Validation and Monitoring

Integrated into the data entry system are real time validations, including both inter- and intra-instrument data checks. Inconsistent or questionable values are flagged during entry, and an edit report is automatically generated to the data entry client. These edit reports provide the

information necessary to investigate any data entry errors or resolved questions regarding out-of-range or questionable values. The eCOS system tracks data entry quality and missing data rates by instrument and data collector.

11.3 Data Security and Integrity

The Web-based components of the data management system utilize several levels of security to ensure privacy and integrity of the study data. Access to data from both inside and outside the DCC is controlled by extensive security features. The archiving and back-up system ensures minimal data loss, even in the most catastrophic system failure. The eCOS database is backed up nightly with backups rotated to a secure offsite facility on a routine basis. Data will not be stored on laptop computers.

11.4 Biospecimen Tracking

Specimen tracking is started from the time of receipt at the site, through shipment to the core laboratory that will assess udenafil plasma concentrations. Each specimen will be labeled with the study code, time of collection, a unique specimen number that is different from the subject's unique study identification (ID) number, and the aliquot number (1 or 2). The master list linking the specimen identification numbers to the subject study ID numbers will be maintained under password protection in the data management system at the DCC. This blinding code system will maintain the confidentiality of the specimens yet allowing linkage of the specimens with clinical study data for analyses.

12. QUALITY CONTROL AND QUALITY ASSURANCE

The DCC has primary responsibility for quality control (QC) / quality assurance (QA) activities of the data. The DCC also requires that the sites complete certain QC activities, most of which are monitored by the DCC. The key QC/QA activities are:

- Development of a Study Manual;
- Clearly formatted and carefully constructed Data Forms with clear, up-to-date manuals of instruction;
- Sign-Off Procedures for all CRFs;
- Central protocol training and tracking of all site data collection staff with the use of standardized checklists;
- Data management training and certification of site personnel completing data entry and/or data management;
- Verification of patient eligibility;
- On-going monitoring of all protocols/data collection activities;
- Inclusion of repeat measurements, as feasible, in the course of the study; and
- Monitoring visits to sites as required with pre-specified goals and/or remote monitoring activities.

The DCC may conduct site visits to the Core Laboratories and/or Biorepository to review QA and QC procedures and data transfer to the DCC. Review of central laboratory-related reports will be conducted at least monthly to identify overall or site-specific problems in data or specimen acquisition and reporting of results.

13. ETHICS AND HUMAN SUBJECTS CONSIDERATIONS

13.1 Potential Risks

Clinical data collection

There are no significant procedural risks associated with physical examination or testing by ECG or echocardiography. These evaluations, however, may rarely reveal previously unknown cardiac abnormalities.

Exercise Testing

Exercise testing is part of the routine care of children and young adults and will be performed with coverage by a pediatric cardiologist. In this study, the subject's heart rate, rhythm, blood pressure, and arterial oxygen saturation will be monitored throughout the exercise test. The subjects will exercise on a cycle ergometer, which minimizes the risk of falling or musculoskeletal injury. The physician or subject may stop the test at any time they feel unable or uncomfortable proceeding. To minimize risk, subjects with either clinical heart failure or a recent history of heart failure or clinically significant arrhythmia will be excluded from the study. In patients with Fontan physiology, the risks of exercise testing in this are low. In the PHN Cross-sectional Fontan Study, there were no complications of exercise testing in 411 subjects[3].

Echocardiogram and EndoPAT® Testing

Echocardiograms are part of routine care for children and young adults with Fontan physiology. Subjects may have minor skin irritation from the patches placed on the skin during the echocardiogram. Additionally, subjects may experience minimal discomfort related to the performance of the echocardiogram and EndoPAT® testing as a result of pressure on the chest or arm during the testing procedures.

Plasma Collection

Minor temporary discomfort may be associated with the removal of blood by venipuncture or through a blood drawing intravenous catheter. There is a risk of bruising, lightheadedness, and a very small amount of bleeding associated with the blood draw.

Heart Monitor

The patch which secures the monitor to the skin may result in local skin irritation or discomfort.

Study Drug: Udenafil

Sildenafil was the first PDE-5 inhibitor approved by the FDA for treatment of pulmonary hypertension in adults. This approval was based on the results of the SUPER 1 study published in 2005[13]. This study included 278 subjects followed for one year. There were two serious adverse events felt to be potentially related to the study drug: left ventricular dysfunction and postural hypotension in one subject each. The most common side effects were headache and flushing. The incidence of side effects is listed in the table below. There was no significant alteration in any monitored laboratory value associated with any dose of sildenafil used in this study.

Incidence of side effects by dosage in adults with pulmonary hypertension SUPER1 Study[13]

Side Effect	**Placebo (N=70)**	**Sildenafil**		
		20 mg (N=69)	**40 mg (N=67)**	**80 mg (N=71)**
Headache	27 (39)	32 (46)	28 (42)	35 (49)
Flushing	3 (4)	7 (10)	6 (9)	11 (15)
Dyspepsia	5 (7)	9 (13)	6 (9)	9 (13)
Back pain	8 (11)	9 (13)	9 (13)	6 (8)
Diarrhea	4(6)	6 (9)	8 (12)	7 (10)
Limb pain	4 (6)	5 (7)	10 (5)	6 (8)
Myalgia	3 (4)	5 (7)	4 (6)	10(14)

Cough	4 (6)		5 (7)		3 (4)		6 (8)
Epistaxis	1 (1)		6 (9)		5 (7)		3 (4)
Pyrexia	2 (3)		4 (6)		2 (3)		7 (10)
Insomnia	1 (1)		5 (7)		4 (6)		3 (4)
Influenza	2 (3)		4 (6)		4 (6)		3 (4)
Visual disturbance	0		0		3 (4)		5 (7)
Gastritis	0		2 (3)		2 (3)		3 (4)
Data presented as N (%)							

Tadalafil was approved more recently based on a study of 405 young adults with pulmonary hypertension from multiple causes. At the 40 mg daily dosage, side effects were similar to SUPER 1 study, only headaches occurred at a significantly higher rate than placebo. There was no clinically significant change in any safety laboratory values. Serious adverse events were equally distributed throughout all treatment arms[25].

There are fewer data on the safety of PDE-5 inhibitor use in children and adolescents[12, 26, 27]. A recent review of pediatric studies by Huddleston et.al. showed that the side effect profile in this population was similar to that reported in the SUPER1 Study. However, the incidence of side effects appears to be significantly lower[26]**.** Similarly to SUPER1, there was no significant change in any monitored laboratory testing with PDE-5 inhibitors in the pediatric population in these small pediatric studies. The recently published STARTS-1 and STARTS-2 trials evaluated three escalating doses of sildenafil in pediatric patients with pulmonary arterial hypertension. Increased mortality was observed in the higher dosage cohorts of the STARTS-2 extension trial[28].

Incidence of side effects of sildenafil in the pediatric population. Pooled data from 15 studies in children[26]

Adverse Event	Description	*n*	Incidence (%)
Hypotension	Significant blood pressure reduction and impaired oxygenation with IV, transient with PO	15	5.9
Erection	Mostly short-lived erection, recurrent	6	2.6
Nasal congestion	Transient, resolved upon discontinuation	6	2.3
Headache	Persistent (sildenafil suspended 4 mo); one only with dose > 125 mg	4	1.6
Dizziness	Resolved with dose reduction; one only with dose > 125 mg	3	1.2
Flushing	Resolved with dose reduction; one only with dose > 125 mg	3	1.2
Bleeding	Circumferential oozing after circumcision requiring cauterization and sutures; penis was erect	1	< 1
Body ache	Mild, self-limiting	1	< 1
Epistaxis	Self-limiting	2	< 1
GI upset	Not otherwise described	2	< 1
Heavy menstrual flow	With menarche, responded to progesterone therapy	2	< 1
Optic neuropathy	Monocular visual loss	1	< 1
Pneumothorax	Questioned relatedness	1	< 1
Retinopathy	Retinopathy of prematurity	1	< 1
Rhinorrhea	Resolved with dose reduction	2	< 1
Intestinal pneumatosis	Temporarily discontinued, safety restarted without other documented adverse event (continued 688 days)	1	< 1

Abdominal discomfort	Not otherwise described	NR	
IV intravenous; PO by mouth, NR not reported % incidence calculated by utilizing sum of all pediatric studies and case reports			

The largest controlled trial of a PDE-5 inhibitor in the pediatric congenital heart disease population, and the only study to assess its use in the Fontan population, is the Sildenafil After the Fontan Operation Study (SAFO Study), which served as the pilot study for this proposal[11]. In this study, 31 subjects underwent a double-blind 6-week cross over study of sildenafil and placebo. Headache and facial flushing were the only 2 side effects that occurred significantly more in the sildenafil treatment arm compared to the placebo. Interestingly, both of these side effects were only more common in the female subjects. Dizziness and vomiting were the only other side effects that occurred in more than 1 percent of the study subjects and were equally common in both treatment arms. These findings are summarized in the table below. Of note, there were no cases of priapism or visual disturbance in this population. These data suggest that PDE-5 inhibitors are well tolerated in the pediatric population with a side effect profile at least as safe as that seen in adults. Summary of Side Effects for the SAFO Study[11].

Event	**Sildenafil (*n* = 27)**	**Placebo (*n* = 28)**
Headache	9 (33%)	5 (18%)
Flushing	5 (19%)	0 (0%)
Dizziness	2 (7%)	2 (7%)
Nausea/Vomiting	2 (7%)	0 (0%)
Abdominal Pain	1 (4%)	0 (0%)
Kidney Stone	1 (4%)	0 (0%)
Photosensitivity	1 (4%)	0 (0%)
Rash	1 (4%)	0 (0%)
Diarrhea	0 (0%)	1 (4%)
Hypotension	0 (0%)	1 (4%)
Muscle Pain	0 (0%)	1 (4%)
Tinnitus	0 (0%)	1 (4%)
Tremors	0 (0%)	1 (4%)
Any Event	19 (70%)	18 (64%)

We are aware of three previous Phase I studies of Udenafil, all performed in healthy adult male populations designed to investigate the safety, tolerability, PK, and PD of Udenafil. In these three studies, there were no serious adverse events. Adverse events were primarily limited to those expected for PDE5 inhibitors and included facial flushing, headache, and spontaneous erection. All of the observed adverse events appeared to occur in a dose responsive manner, with the majority of events occurring at doses of 200 mg or more. The side effect profile reported in these three studies is similar to that reported in the pilot trial of sildenafil (20 mg three-times daily) in the Fontan population, in which the most common adverse events were headache and flushing[11]. In studies of PDE5 inhibitors in the Fontan population, there were no unanticipated side effects. It is important to confirm that the short-term safety and tolerability of udenafil before starting a RCT in this cohort. For this reason a Phase I/II dose escalation trial of udenafil in adolescents with Fontan palliation has been completed prior to this study to establish safety and dosage for this study. The adverse events associated with the escalated dosages in this study are presented in **Table 3**. For the 87.5 mg BID dose to be used in the current study, headache, flushing, and spontaneous penile erection were present in percentages similar to the previous pediatric studies reported above.

Table 3. Drug-related *adverse events that occurred more than once in one subject or in more than one subject in at least one cohort

Preferred Term, #Events (#Subjects)	37.5 mg daily (N=6)	37.5 mg twice daily (N=6)	87.5 mg daily (N=6)	125 mg daily (N=6)	87.5 mg twice daily (N=6)
Abdominal discomfort	0 (0)	0 (0)	0 (0)	3 (1)	1 (1)
Back pain	0 (0)	0 (0)	0 (0)	0 (0)	4 (1)
Flushing	2 (1)	2 (2)	4 (4)	1 (1)	7 (2)
Headache	8 (3)	6 (4)	9 (4)	13 (4)	12 (4)
Nasal congestion	1 (1)	2 (2)	1 (1)	1 (1)	3 (1)
Nausea	1 (1)	2 (1)	0 (0)	0 (0)	1 (1)
Spontaneous penile erection	0 (0)	2 (1)	1 (1)	2 (2)	6 (2)

*Probably or possibly; definitely related

13.2 Confidentiality, Protection against Risks

Investigators will take all reasonable measures to protect the confidentiality of subjects and their families, including the following:

Use of Subject ID numbers

Each subject is assigned a subject identification number (SID). All interview and clinical research data are stripped of identifiers and labeled with the study number. The enrollment log with participant identifiers will be maintained at each site in a secured, locked location available only to the study staff. Samples for DNA will be stripped of the study SID at the laboratory and assigned distinct specimen numbers without other identifying information. The informed consent form states that study data will be made available to the DCC and NIH/NHLBI to ensure study safety and quality control. The subject's name and any other identifying information will not appear in any presentation or publication resulting from this study.

Reporting of Test Findings

The results of future tests on biological specimens will not be released to the subject/family. At the end of the study, the results of the genetic testing may be published for all the subjects as a group, but it will not be possible to provide results for an individual subject and medical management will not be changed based on individual results. There is a reasonable possibility that no findings will result from this research effort. If findings are detected, it may be years before any utility of these findings is realized. Further, if samples are "anonymized" prior to release to other investigators for research, it may not be possible to trace the results back to the subject.

If an incidental finding is found on a study clinical test, the PI or other qualified member of the research team will take full responsibility for disclosing the findings to the patients/parents, communicating with their primary cardiologist with permission, or making appropriate cardiology referrals as indicated. The subject may choose to seek a second opinion and/or appropriate clinical care. This might change the subject's insurability and employability as it relates to the clinical finding only. The presumption is that detection of a potentially clinically significant finding will prove to be beneficial.

Certificate of Confidentiality

To help us protect the privacy of subjects who provide biological specimens and to be compliant with current NIH policy, we will obtain a Certificate of Confidentiality from the National Institutes of Health (NIH). With this Certificate, the researchers of this study cannot be forced to disclose information that may identify a subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The Certificate cannot be used to resist a request for information from the United States government when it is used for evaluating federally funded study projects or for information that must be disclosed to meet the requirements of the Food and Drug Administration (FDA). A Certificate of Confidentiality does not prevent a subject or his/her family from voluntarily releasing information about the subject's involvement in this research. If an insurer, employer, or other person obtains a subject's or family's written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

Information from DNA analyses and phenotypic data from clinical studies or medical records may be placed into a central data repository in the future, such as the National Center for Biotechnology Information repository. Data and samples will be de-identified before submission to this or any other central repository.

Exercise Testing

Exercise testing will be performed in the presence of a cardiologist. The subject's heart rate, rhythm, blood pressure, and arterial oxygen saturation will be monitored throughout the study. The subjects will exercise on a cycle ergometer which minimizes the risk of falling or muscular-skeletal injury. The physician or subject may stop the test at any time they feel unable or uncomfortable proceeding. To minimize risk, subjects with either clinical heart failure or a recent history of heart failure will be excluded from the study.

Risk of Udenafil

Any subject with a previous serious adverse reaction to a PDE-5 inhibitor or a known contraindication to its use will be excluded from this study. Incidence of side effects will be monitored at every study visit. Subjects and families will be encouraged to report any serious event to study personnel as soon as the event occurs, rather than waiting for scheduled visits or phone calls.

13.3 Potential Benefits

There are potential benefits to participating in this study. The observed decline in exercise capacity in adolescents with Fontan physiology is substantial and well documented. It is clear that a significant percentage of this population will have an aerobic capacity with exercise testing that is below 45% - 50% of predicted by their third decade of life. When this level of exercise intolerance is reached, the risk of overt heart failure, hospitalization, and death or transplantation rises significantly. If udenafil improves aerobic capacity, this may prolong by years the time to onset of overt symptoms in this population. However, udenafil can only be used clinically if it is determined to be safe.

Currently, there is no known direct benefit from provision of biospecimens by the subject and family. The indirect benefit comes from the potential knowledge about the relationship between genetic factors or biomarkers and longer-term cardiac and neurodevelopmental outcomes. This information may help physicians provide better answers to families' questions regarding causes, risk, and recurrence risks. It may also inform development of future interventions and/or treatments.

13.4 Risk/Benefit Ratio and Importance of Information to Be Obtained

The risk/benefit ratio of the study is favorable. The risk of adverse drug reactions is low, and most are relatively minor in nature and reversible with a decrease in the dose of study drug or cessation of therapy. The results of this study and the information that it provides will allow for the design of a randomized clinical trial to study the impact of udenafil in the Fontan population.

14. STUDY LIMITATIONS

This study will evaluate the safety of udenafil in a large cohort of adolescents over a one-year time period and may therefore fail to identify side effects that occur over a longer period of time. As such, ongoing surveillance of udenafil in the population is recommended if this drug were to be adopted for routine clinical use.

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