Rhode Island Diastolic Dysfunction – Heart Failure (RIDD-HF)

NCT02353312

9/22/2016

Study Title: Rhode Island Diastolic Dysfunction – Heart Failure (RIDD-HF)
Primary Investigator: Wen-Chih Wu
Version Date: 12/12/14; 2/10/15, 5/10/16, 9/22/16

Rationale:
Congestive heart failure carries a significant epidemiologic and economic burden in today's healthcare system and is associated with increased morbidity and mortality in those affected. There are approximately 5 million people in the United States with heart failure, and of those, nearly half have heart failure with preserved ejection fraction (HFpEF)[1]. HFpEF, also referred to as diastolic heart failure, is a clinical syndrome characterized by prolonged relaxation of the myocardium resulting in symptoms including dyspnea, edema, fatigue, and decreased exercise tolerance, which are clinically indistinguishable from the presentation of heart failure with reduced ejection fraction (HFrEF). The underlying mechanisms in diastolic dysfunction are not clearly elucidated, making targeted therapy a challenge[2]. There are currently no FDA approved treatments for this syndrome, and multiple clinical trials have demonstrated that standard treatments for systolic heart failure are ineffective in treating diastolic dysfunction [3-6]. The current standard of care for HFpEF includes blood pressure control with beta-blockers, ACE inhibitors, and angiotensin receptor blockers (ARBs) in accordance with current clinical practice guidelines, as well as the use of diuretics for management of symptoms due to volume overload.

One of the proposed underlying mechanisms of diastolic dysfunction is via the reduction of nitric oxide (NO), an endothelium-derived vasodilator that regulates blood pressure and regional blood flow[7]. In 2010, Silberman et al. examined the effect of cardiac oxidation on nitric oxide and found that depletion of tetrahydrobiopterin (BH4), an essential cofactor in the production of nitric oxide, causes uncoupling of nitric oxide synthase, impaired relaxation of cardiac myocytes, and leads to subsequent diastolic dysfunction. The authors further went on to demonstrate that treatment with BH4 can improve diastolic dysfunction in a hypertensive mouse model as well as in isolated cardiac myocytes and may play a role in the treatment of HFpEF[8].

Kuvan®(sapropterin dihydrochloride) is a synthetic form of the cofactor BH4 (tetrahydrobiopterin) for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates phenylalanine to form tyrosine. BH4 activates residual PAH enzyme, improving normal phenylalanine metabolism and decreasing phenylalanine levels in responders. Kuvan®(sapropterin dihydrochloride) was approved by the US Food and Drug Administration (FDA) in 2007 for use in treatment of the genetic disorder phenylketonuria at doses of 5-20mg/kg once daily. To our knowledge, the role of Kuvan®(sapropterin dihydrochloride) in treating diastolic dysfunction in human subjects has not been studied.

Hypothesis:
Treating patients with underlying diastolic dysfunction with Kuvan®(sapropterin dihydrochloride), in addition to standard care for heart failure will improve metabolic parameters and echocardiographic parameters of diastolic function compared to standard care for heart failure alone

Specific Aims:

Primary Aim:

Study the effect of Kuvan®(sapropterin dihydrochloride) supplementation in addition to standard care for heart failure compared to standard care alone on maximum VO2 consumption in patients with diastolic dysfunction from baseline to three months on medication. This parameter will be obtained via cardiopulmonary exercise stress testing.

Secondary Aim:

Study the effect of Kuvan®(sapropterin dihydrochloride) supplementation in addition to standard care for heart failure compared to standard care alone on additional metabolic parameters obtained from CPET (Ve/VCO2), echocardiographic parameters of diastolic dysfunction (see below), and quality of life (measured by Kansas City Cardiomyopathy Questionnaire) for the duration of the study.

Relevance to VA:

The functional and economic burden of congestive heart failure on the Veterans' health system is unparalleled. It is the number one reason for admission in this system, with over 100,000 hospitalizations for this diagnosis and a re-admission rate of near 20% in the last fiscal year. Additionally, it accounted for over 1,000,000 outpatient encounters over the same time period[9]. The cost of this disease is greater than $37 billion to the United States healthcare system[10]. Accordingly, The CHF Quality Enhancement Research Initiative [QUERI] was created to improve both survival and quality of life in veterans with heart failure. The efforts of this initiative have been focused on systolic dysfunction, due to the paucity of positive studies on diastolic dysfunction. If successful, our study will improve the quality of life and outcomes for the large number of veterans affected by this disease.

Study Design

This proposal describes a randomized crossover pilot study in 30 subjects at the Providence VA Medical Center to address the hypothesis that Kuvan®(sapropterin dihydrochloride) supplementation is an effective treatment strategy in patients with heart failure with preserved ejection fraction. The subjects will be randomized into two groups; Kuvan®(sapropterin dihydrochloride), in addition to best current clinical practices versus best current clinical practices alone. The randomization process will occur in a one to one fashion. At the end of three months, there will be a wash out period of one week (during which both groups will not take the study medication) prior to the groups being crossed over. Data will again be collected and reviewed at monthly intervals and at the end of the study.

Inclusion Criteria

1. Male and female U.S. Veteran patients over the age of eighteen, with echocardiographic findings of >= Grade 2 diastolic dysfunction [as per American Society of Echocardiography guidelines] and
2. Diagnosis of hypertension, diabetes (type 1 or type 2), or heart failure in medical records.

3. Eligible subjects must be ambulatory (not dependent on any ambulatory assist devices including cane or walker).

Exclusion Criteria

1. Any history of documented ejection fraction <50%
2. Significant COPD (defined as oxygen-dependent COPD)
3. Acute coronary syndrome within the past three months defined by EKG changes and biomarkers of myocardial necrosis (ie. elevated troponin) in the setting of chest pain or an anginal equivalent)
4. Presence of hypertrophic cardiomyopathy
5. Presence of infiltrative/restrictive cardiomyopathy
6. Echocardiographic evidence of moderate or severe aortic or mitral valve stenosis or regurgitation
7. Bioprosthetic or mechanical valves
8. Use of medication that effect folate metabolism (e.g. Methotrexate, pralatrexate)
9. Previously diagnosed phenylketonuria
10. Previously diagnosed BH4 deficiencies
11. End stage renal disease requiring hemodialysis
12. Pre-existing seizure disorder
13. Terminal illness (not including heart failure) with expected survival of one year or less
14. Females who are pregnant or breastfeeding. All females of child bearing age will undergo pregnancy testing prior to randomization.
15. Recent hospitalization within three months.

Source of Participants and Participant Recruitment:

Patient recruitment will occur at the site of the Providence VAMC by echocardiographic database and medical chart search. A population of potential study patients will be generated, which will identify patients with echocardiographic parameters of diastolic dysfunction without evidence of systolic dysfunction. Subsequently, a chart review of the electronic medical record system [CPRS] will be performed on potential patients to evaluate for inclusion and exclusion criteria. Potential subjects will be temporarily recorded in a password protected spreadsheet in a restricted access folder on a VA secure server. Personal identifiers of subjects who do not participate will be deleted from the database. We will be requesting an IRB waiver of HIPAA and informed consent for screening purposes ONLY.

After subjects are identified by screening of the database and chart review, subjects will be sent a letter informing about the study. The letter will contain a return envelope to notify us within 15 days of the mailing date if the subject does not want to be contacted by phone. If we do not receive the refusal letter, subjects will be contacted by telephone and will be provided basic information regarding the study. Patients who are interested in participating will be scheduled for a screening visit.

Study Visits (Total of 7 Study Visits and 5 Telephone Calls)
The study visits will take place in patient exam rooms in either the main hospital (building l) ,research buildings 32 or 35.

1. Screening visit:
At this visit, the study will be explained in detail to the patient, and inclusion and exclusion criteria will be reviewed by the study team members. If the patient meets the eligibility criteria and is willing to participate, written informed consent will be obtained. Following the completion of informed consent, the subjects will undergo a limited history and physical exam.

Blood will be drawn for measurement of basic chemistry panel, complete blood count, fasting lipid panel, liver function tests, and the following biomarkers: BNP, glutathionylated myosin binding protein C, adiponectin, aldosterone, endothelin-1, NT-procollagen III, uric acid, and derivatives of reactive oxygen metabolites (DROM). These blood tests have been examined in various studies as markers of the presence of heart failure, ability to respond to treatment of heart failure, or early diagnosis of heart failure[11-15].

Subjects will then receive a weight-based test dose of 10mg/kg (rounded to the nearest hundred) of the study medication (Kuvan®(sapropterin dihydrochloride),) and the subject will be observed with blood pressure and oxygen levels being recorded every thirty minutes for one hour. If at any point during this time period, the subject develops hypotension (Systolic Blood Pressure [SBP] <90 or a drop in SBP >20mmHg with associated dizziness or syncope), hypoxemia (decrease in oxygen saturation to <90% on room air), or any evidence of an allergic reaction (pruritus, rash, hives, Heart Rate>100, abdominal cramping, nausea, emesis, or angioedema), the subject will not participate further in the study. Subjects experiencing any of the above symptoms will receive appropriate monitoring and clinical care, potentially including hospital admission, supplemental oxygen, IV fluids, until they are stabilized.

The patients who tolerate the test dose will complete the Kansas City Cardiomyopathy Questionnaire and receive a baseline echocardiogram.

Informed Consent Procedure:
Members of the investigator team will explain the study to the potential participants and answer any questions that they may have regarding the study protocol. The investigator will make it clear that the protocol is research as well as voluntary and that declining participation will in no way affect further evaluation or access to clinical care. Participants will also be informed that they may withdraw their consent at any point throughout the study. Patients will be given adequate time to read the consent form and discuss its contents with research personnel before signing the consent form. They will also be provided with a phone number through which adverse events should be reported. Participants will then be asked to sign an IRB-approved written consent document and health insurance portability and accountability act (HIPAA) agreement, which will allow data pertinent to the study to be collected.

Following the completion of informed consent, the baseline visit will be scheduled within one week of study enrollment.

2. **Baseline visit**:
At this visit, the subjects will undergo a brief interview to assess for recent changes in health status. Cardiopulmonary exercise testing will be performed to establish the subjects' baseline. The patients will then be randomized (in a 1:1 fashion as mentioned above) to either Group 1, who will begin the study by taking the study medication in addition to their current medication regimen, or Group 2, who will begin the study by continuing their current medication regimen without the study medication. The subjects in Group 1 will be provided with their preference ofeither a supply of 100mg Kuvan®(sapropterin dihydrochloride) tablets or Kuvan®(sapropterin dihydrochloride) in the powder form. This visit will last three hours.

The subjects in Group 1 will be instructed to initiate the study medication at the weight-based dose of 10mg/kg (rounded to the nearest hundred) with meals (at the same time each day) for one week beginning the following day (day 1). After telephone contact (table 2) with a study team member on day 7, assuming no adverse effects are noted, the patient will be instructed to increase their daily dose to 20mg/kg (rounded to the nearest hundred) with meals (at the same time each day) for the remainder of the study period. The subjects in Group 2 will not be started on the study medication until after the 'wash-out period' as described in the study design

Study Drug:
Kuvan®(sapropterin dihydrochloride) is the synthetic form of the naturally occurring essential cofactor BH4 that is FDA approved for the treatment of phenylketonuria at the recommended dose of 10-20mg/kg daily. This study **does not require an IND waiver** as set forth **by the FDA guidelines listed below**:

"The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part [investigational new drug application] if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of 312.7."

The study drug will be provided by BioMarin (Committee decision letter attached below – Appendix A)

Compliance will be assessed by monitoring pill counts with the assistance of the research pharmacist.

Follow up visits:
Patients will attend routine follow up visits as outlined below. These visits will occur within one week of the proposed outlined schedule. At all study visits, a brief history and physical exam will be performed and subjects will be evaluated for medication compliance, adverse reactions, and exacerbation history. In addition, interim ED visits and hospitalizations will be assessed for. Any exacerbations of heart failure, defined as worsening in dyspnea (including orthopnea or paroxysmal nocturnal dyspnea), Jugular Venous Pressure elevation, significant weight gain (>3 lbs in 3 days) or lower extremity edema will be recorded.
Summary of follow up visits is as follows:

6 week visit (thirty minutes) – Brief history and physical exam

12 week visit (three hours)- Brief history and physical exam, Kansas City Cardiomyopathy Questionnaire, labwork for biomarkers (as documented above), chemistry, lipid, and liver panels, BNP, echocardiogram, and CPET testing.

13 week visit (thirty minutes)- Patients will be crossed over to the second arm of the study. They will receive a brief history and the second group will be provided with a supply of Kuvan®(sapropterin dihydrochloride) tablets or powder.

19 week visit (thirty minutes)- Brief history and physical exam.

25 week visit (three hours)- Brief history, Kansas City Cardiomyopathy Questionnaire, labwork for biomarkers, chemistry, lipid, and liver panels, BNP, echocardiogram, and CPET testing.

Telephone calls will be made at week 1, 3, 9, 16, and 22 to assess for patient compliance, provide any necessary support, and screen for side effects.

	Screening Visit	Baseline Visit	Week 1	Week 3	Week 6	Week 9	Week 12	Week 13	Week 16	Week 19	Week 22	Week 25
Contact	Clinic	Clinic	Tel	Tel	Clinic	Tel	Clinic	Clinic	Tel	Clinic	Tel	Clinic
Limited History/ Physical	x				x		x	x		x		x
Assess Medication Compliance					x		x			x		x
Labwork	x						x					x
Echo	x						x					x
CPET		X					x					x
KCCQ	x						x					x
Exacerbation History		x	x	x	X	x	x	x	x	x	x	x
Adverse Event Monitoring			x	x	X	x	x	x	x	x	x	x

Table 1. Follow-up Clinic Visits, telephone calls, and schedule of studies. CPET, cardiopulmonary exercise stress test; KCCQ, Kansas City Cardiomyopathy questionnaire; Tel, telephone contact; Labwork: basic chemistry panel, complete blood count, lipid panel, liver function tests, and the following biomarkers: BNP, glutathionylated myosin binding protein C, adiponectin, aldosterone, endothelin-1, NT-procollagen III, uric acid, DROM

Subject Reimbursement:

Subjects will be reimbursed for every visit they attend. Attendance to visits 1 and 2 (screening and baseline visits), as well as visits 4 and 7 (all three hour visits) will be reimbursed fifty dollars. Attendance to visits 3, 5, and 6 will be reimbursed twenty-five dollars.

Specific Study Procedures:

Questionnaire: The Kansas City Cardiomyopathy questionnaire will be used and is attached (Appendix B).

Echocardiogram: Transthoracic echocardiography uses ultrasound technology to evaluate heart structure and function. Measurements to be collected include:

1. Tissue Doppler Index (Septal and Lateral E')
2. E Velocity
3. E/E' ratio
4. E/A Ratio
5. Pulmonary Vein Tracing (S/D Ratio, A-AR duration, AR Velocity)
6. Deceleration Time
7. Pulmonary artery systolic pressure
8. Right Ventricular Function (assessed by TAPSE)
9. Left Ventricular Mass
10. Left Atrial Volume Index
11. Longitudinal Strain
12. Circumferential Strain
13. Strain Rate

All echocardiograms will be reviewed by two independent echocardiographers.

Cardiopulmonary exercise test:
Cardiopulmonary exercise testing is a test of a subject's maximal exercise capacity. This test will be performed at the Providence VAMC on clinical VA owned equipment. This test will be performed on a bicycle in the presence of a physician. The subject will wear nose clips, and will breathe through a mouthpiece connected to a metabolic machine, which will measure factors including oxygen consumption, CO2 production, volume of air per breath, and respiratory rate. The patient will also be monitored by EKG leads demonstrating the heart rate and rhythm. The patient will then exercise at increasing levels of resistance (increasing intensity of exercise) according to a protocol until the protocol is completed or the patient can no longer exercise. The maximal value for oxygen consumption (VO2 max) will be recorded, along with other exercise parameters such as the respiratory quotient (ratio of O2 consumption to CO2 production), the ventilatory equivalent ratio for carbon dioxide (Ve/VCO2), and the dead space to tidal volume ratio.

Laboratory testing:
This will be done by a trained phlebotomist who will draw blood samples from a venipuncture site, typically from the subject's arm. The laboratory tests drawn include a, basic serum chemistry panel, lipid panel, liver panel, and biomarkers associated with diastolic dysfunction (as described above). All labs, besides the diastolic dysfunction biomarkers are basic labs and will be drawn and handled at the Providence VA per VA laboratory protocol. The labs associated with diastolic dysfunction will be drawn by phlebotomy but handled by the protocol below:

1) Draw six lavender top (EDTA) tubes (2 tablespoons each). These tubes will be maintained at 4°C.
2) 1cc of whole blood will be aliquotted from the 1st tube and transferred into the plain orange-screw-top cryo tubes.
3) Then, the tube will be balanced and centrifuged at 2000g for 10 min using refrigerated centrifugation.
4) 1cc plasma to orange top cryo tubes and stored at -80°C freezer until use. This blood will be stored in Dr. Choudhary's (co-investigator) storage area

Blood Samples Transfer see: Protocol Addendum: Information Privacy and Security Items and Safety

Patient safety:

Human Subjects Research
This Human Subjects Research meets the definition of "Clinical Research". This study is a clinical trial, and will be registered on Clinicaltrials.gov.

Protection of human subjects
Potential risks
Questionnaires and record keeping. There is no specific physical risk to completing the quality of life questionnaires. All records will be kept confidential, kept in locked cabinets, and identified by study code only in the working databases.

Phlebotomy. Phlebotomy for blood drawing is associated with temporary pain at this site and may result in bruising at the needle insertion site. Risks of the procedure include: vasovagal reaction during needle puncture; bruising at the phlebotomy site; and the possibility of skin or soft tissue infection at the needle puncture site.

Echocardiogram. Standard approaches to performing transthoracic echocardiography will be utilized, which may induce transient discomfort as the ultrasound probe is pressed against the upper chest.

Cardiopulmonary exercise testing. The testing may cause shortness of breath, fatigue, muscle discomfort, and very rarely (<1:1,000) may be associated with heart attack or death.

Therapeutic risks
Treatment with Kuvan®(sapropterin dihydrochloride).
Kuvan®(sapropterin dihydrochloride) is currently FDA approved for the treatment of phenylketonuria (PKU). The most common side effects include: headache, peripheral edema, arthralgia, polyuria, agitation, dizziness, nausea, pharyngitis, abdominal pain, upper abdominal pain, and upper respiratory tract infection.

In clinical trials the most common adverse reactions (≥4% of patients) were: headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, vomiting, cough, and nasal congestion.

In the postmarketing period, the most common adverse reactions due to Kuvan are oropharyngeal pain, pharyngitis, esophageal pain, gastritis, dyspepsia, abdominal pain, nausea and vomiting. Hypersensitivity reactions including anaphylaxis and rash have been reported. Most hypersensitivity reactions occurred within several days of initiating treatment. Two cases of hyperactivity have been reported, including one case in a patient who received an accidental overdose of Kuvan.
Kuvan®(sapropterin dihydrochloride) has not been tested in pregnant women, and there may be unknown risks for pregnant women and for their developing embryo, fetus, or unborn child. The package insert for Kuvan®(sapropterin dihydrochloride) is included in Appendix C.

Protection against risk
Study personnel will be fully trained and credentialed in human subjects protection. Study ID numbers will not include PHI. All research data which will be kept in locked cabinets or password protected files on VA servers.

Risks from cardiopulmonary exercise testing will be minimized by supervision of testing by an attending physician, fellow/resident, or trained technicians at VA Providence with emergency equipment readily available. Patients will be encouraged to exercise to their symptomatic limits, if there are any signs of medical instability, the physician will end the test before the symptomatic endpoint is achieved.

Phlebotomy will be performed by trained phlebotomists.

Females of reproductive age will undergo pregnancy testing prior to receiving the study drug as per the previously noted exclusion criteria. Female subjects will be instructed to use an effective form of contraception during the study period. If any female subjects become pregnant during the study, they will immediately stop taking the study medication and inform their study physician.

Social Risk:
There is a mild risk of inadvertent loss of confidentiality if the computer files or paper files where the patient protected health information or identifiers are breached by vandalism or when regulatory agencies or committees at Providence VAMC or Lifespan reviews the patient records. This risk will be minimized by assigning a study patient ID and saving all protected health information separate from patient files that contain the key with the identifiers. This key will be saved in a password protected file. All paper forms (informed consent, data collection forms, study binders) will be saved in a locked cabinet within Dr. Wu's office. Only study personnel will have access to these files.

Potential benefits of research to human subjects and others
The potential benefit of Kuvan®(sapropterin dihydrochloride) includes improvement of quality of life by decreasing symptoms of heart failure as well as delaying pathophysiologic progression of disease. If the administration of Kuvan®(sapropterin dihydrochloride) does not accomplish these goals, then there may be no direct clinical benefit to the subjects. However, in such case our results will demonstrate that

Kuvan®(sapropterin dihydrochloride) supplementation is not a useful therapy in the treatment of Heart Failure with preserved Ejection Fraction.

Importance of knowledge gained

As detailed above, heart failure with preserved ejection fraction remains a therapeutic dilemma and plays a significant role in the growing cost of health care due to hospital admissions and readmissions. Further, there are no established treatments that have been proven to improve the morbidity and mortality associated with this syndrome. The benefits to this study include establishing new data regarding the treatment of HFpEF. If Kuvan®(sapropterin dihydrochloride) supplementation is successful in improving symptoms and outcomes in this patient population, this study will be an important step towards a novel treatment for HFpEF. However, if this medication is ineffective in our subjects, then this study will argue against the use of Kuvan®(sapropterin dihydrochloride) for treatment of this disease.

Data and safety monitoring

Patients will be contacted via phone at weeks 1, 3, 9, 16, and 22. During these phone calls, patients will be asked the questions outlined in Table 2. Additionally, the patients will be seen in person in a research clinic during weeks 6, 12, 13, 19, and 25. At these clinic visits, patients will be asked the questions listed in Table 3. The research team will meet every 4 weeks to review study progress and adverse events. Additionally, all data will be reviewed to assure that no physiological findings warrant immediate intervention. If so, the participant will be contacted and advised of the findings and offered assistance with appropriate referrals. Data from the echocardiogram, laboratory tests and cardiopulmonary exercise testing procedures will be reviewed by the investigators and any unusual or adverse findings will be communicated to the participant's primary care physician. Adverse events will be defined as per the BioMarin Standard Language for Adverse Event Report (below, and attached in Appendix D) and reported to the IRB in accordance with the rules regulating each severity class (expected vs. unexpected, serious vs. other, related vs. unrelated).

BioMarin Standard Language for Adverse Event Reporting: IST Program, Kuvan

According to the ICH definition, an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the investigational product.

This definition includes intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions. Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

Adverse event information will be collected in an ongoing fashion through patient reporting AEs to their physician or health care provider. Seriousness and relatedness will be assessed by the treating physician, with appropriate reporting.

A designated primary contact person based at the treatment center will be responsible for the collection and reporting of AEs for patients participating in the program.

Serious Adverse Events

A serious adverse event (SAE) is defined as any AE that:

- Results in death
- Is life threatening, that is, places the subject at immediate risk of death from the event as it occurred. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death
- Requires in-patient hospitalization or prolongation of an existing in-patient hospitalization. Admission of a subject to the hospital as an in-patient as a result of an AE, even if the subject is released on the same day, qualifies as hospitalization
- Results in persistent or significant disability or incapacity. An event qualifies as resulting in a persistent or significant disability or incapacity if it involves a substantial disruption of the subject's ability to carry out usual life functions. This definition is not intended to include experiences of relatively minor or temporary medical significance.
- Is a congenital anomaly or birth defect, an AE that occurs in the child or fetus of a subject exposed to the product prior to conception or during pregnancy
- Important medical event that does not meet any of the above criteria, but may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed above.

More than one of the above criteria may apply to any specific event.

Pregnancy

Pregnancy in a subject being treated with the product should be reported immediately (within 24 hours of becoming aware of the pregnancy) to BioMarin Pharmacovigilance by using the FDA 3500A (MedWatch Form). Every effort should be made to follow the patient through resolution of the pregnancy (termination or delivery) and report the resolution of the FDA 3500A (MedWatch Form) to BioMarin Pharmacovigilance.

SAE and Pregnancy Reporting

All serious adverse events (SAEs) and pregnancy reports whether or not considered drug-related should be reported to BioMarin Pharmacovigilance within 24 hours of receipt by the investigator/sponsor by using the FDA 3500A (MedWatch Form).Clinicians should not wait to collect additional information that fully documents the event before notifying BioMarin's Pharmacovigilance Department of an SAE or pregnancy. BioMarin may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore it is important that clinicians submit additional information requested by BioMarin Pharmacovigilance as soon as it becomes available.

Reporting of SAEs to the IRB will be done in compliance with the standard operating procedures and policies of the IRB and with applicable regulatory requirements.

Follow up visits:
Patients will undergo routine follow up visits as outlined in Table 1 to assess compliance with medication use, changes in symptoms, development of adverse reactions and further data collection.

Monitoring for Adverse Events (AEs)
At the baseline clinic visit and each follow-up contact, subjects are to notify study staff if they experience any change in their medical condition or medications, or have urgent care visits, emergency room visits, or hospitalizations. Study staff will also monitor for interim emergency room visits or hospitalizations through patient notification system in CPRS to ensure timely reporting. The investigator will contact participants if any reported adverse event suggests clinical deterioration warranting immediate medical attention. During the study, if a subject experiences medical problems or hospitalization, the study medication will be continued unless complicated by symptomatic hypotension. If discontinued, it would be resumed once baseline clinical status is confirmed, assuming the event was not felt to be related to the study medication itself.

Any adverse events that are immediately life-threatening, cause permanent or lasting harm, or require a hospitalization will receive a "serious" classification as per defined by the BioMarin Standard Language for Adverse Event Report (above, and Appendix D). All serious AEs and unanticipated problems will be reported to the IRB as soon as possible, but no later than 5 days from notification. If an event is possibly, probably or definitely related to the intervention, it will be classified as intervention-related. Any incidental finding discovered during follow up visits or imaging will be graded based on level of severity. Severe findings (as determined by evaluating physician) will be referred to the Emergency Department for further evaluation. Findings determined to be low or moderate severity will be relayed to both the subject and his or her primary care physician or cardiologist.

Sample size determination
Primary Aim:
This study is a pilot study, and as a result a sample size determination is not necessary.

Data Collected see: Protocol Addendum: Information Privacy and Security Items and Safety

Data Analysis Plan see: Protocol Addendum: Information Privacy and Security Items and Safety

Aim 1: The primary outcome will be the difference in maximum VO2 consumption obtained from a cardiopulmonary exercise test at baseline, 3 months and conclusion of the study [ΔVO2 consumption] between Kuvan®(sapropterin dihydrochloride) use versus not. Descriptive statistics (mean, standard deviation, median, inter-quartile range, and frequency distribution) will be calculated to summarize, at baseline, participants' demographic and medical history, and the primary outcome of interest (peak Vo2) according to randomized intervention sequences. We will ensure a balanced randomization is accomplished using t or nonparametric (Wilcoxon's) tests whenever

each test's distribution assumption is appropriate. We will use the variants of statistical methods (t tests and linear models) specifically designed to analyze crossover clinical trials to assess changes in peak VO2 in response to Kuvan®(sapropterin dihydrochloride) supplementation in addition to current best practices versus current best practices alone.

Secondary Aims: The CPET measures and molecular biomarkers will be analyzed using the same crossover analysis models for crossover clinical trials[16].

Data storage and sharing see: Protocol Addendum: Information Privacy and Security Items and Safety

Table 2 - Telephone Monitoring:

Side Effects – fevers, nausea, vomiting, diarrhea, rhinorrhea?
Compliance and barriers to compliance?
Have there been changes in previous medication regimen?
Weight loss/gain?
Is dyspnea improved, worse, or unchanged?
Is there any subjective change in exercise tolerance?
Have there been any doctor's visits or hospitalizations?

Table 3 - Brief History and Physical:

Vital Signs:
Temperature
HR
Respiratory Rate
Oxygen Saturation
Weight
Limited Exam:
HEENT: JVD
CVS: S3
Chest: Crackles
Abd: HJR, Pulsatile Liver
Ext: Edema?
Side Effects – fever, nausea, vomiting, diarrhea, rhinorrhea?
Compliance and barriers to compliance?
Have there been changes in previous medication regimen?
Weight loss/gain?
Is dyspnea improved, worse, or unchanged?
Is there any subjective change in exercise tolerance?
Have there been any doctor's visits or hospitalizations?

References

1) Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003;289:194 –202.

2) Ouzounian M, Lee DS, Liu PP. Diastolic heart failure: mechanisms and controversies. Nat Clin Pract Cardiovasc Med. 2008;5:375–386.

3) Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF Jr, Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. Circulation. 2006;114:397– 403.

4) Hernandez AF, et al. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Life-saving Treatment in Hospitalized Patients with Heart Failure) Registry. J Am Coll Cardiol. 2009; 53:184-192

5) Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359:2456 –2467.

6) Pitt B, et al. Spironolactone for Heart Failure with Preserved Ejection Fraction. N Engl J Med 2014; 370:1383-1392

7) Ziolo MT, Kohr MJ, Wang H. Nitric oxide signaling and the regulation of myocardial function. J Mol Cell Cardiol. 2008;45:625–632.

8) Silberman GA, et al. Uncoupled Cardiac Nitric Oxide Synthase Mediates Diastolic Dysfunction. Circulation 2010; 121: 519-528.

9) Heidenreich, et al. Forecasting the Impact of Heart Failure in the United States: A Policy Statement from the American Heart Association

10) Heidenreich, Paul. The Burden of Heart Failure. http://www.queri.research.va.gov/chf/products/nurse_education/Burden-of-Heart-Failure.pdf

11) de Boer , RA, Voors, AA, Muntendam, P, van Gilst, WH, & van Veldhuisen, DJ. Galectin-3: a novel mediator of heart failure development and progression.". European journal of heart failure 2009; 11 (9): 811–817.

12) Ky B, French B, McCloskey K, Rame JE, McIntosh E, Shahi P, Dries DL, Tang WH, Wu AH, Fang JC, Boxer R, Sweitzer NK, Levy WC, Goldberg LR, Jessup M, Cappola TP (March 2011). "High-sensitivity ST2 for prediction of adverse outcomes in chronic heart failure". Circ Heart Fail 4 (2): 180–7.

13) Takano H, Obata JE, Kodama Y, et al. Adiponectin is released from the heart in patients with heart failure. Int J Cardiol. 2009; 132: 221-226

14) Bishu K, Deswal A, Chen HH, et al. Biomarkers in acutely decompensated heart failure with preserved or reduced ejection fraction. Am Heart J. 2012 Nov; 164(5): 763-770

15) Jeong, EM, Monasky M, et al. Tetrahydrobiopterin improves diastolic dysfunction by reversing changes in myofilament properties. J Mol Cell Cardiol. 2013 Mar; 56:44-54.

16) Senn S. Cross-over trials in clinical research. Second Edition. Wiley; 2002.