SYNOPSIS

Protocol Title: Treatment of Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy

IND Number: 77461

IND Holder: National Heart Lung and Blood Institute (NHLBI)

Responsible Party: Jonathan Goldsmith, MD

Study Site(s):
Children's Hospital, Oakland
Children's Hospital, Pittsburgh
Albert Einstein College of Medicine/Columbia University Medical Center, New York
Howard University, Washington D.C.
Imperial College London and Hammersmith Hospital, London
Johns Hopkins University, Baltimore
NHLBI (intramural), Bethesda
University of Colorado, Denver
University of Illinois, Chicago

Phase of Development: Post-marketing, Phase II/III

Objectives:

Primary Objective(s):

In a randomized, double-blind, placebo-controlled phase II/III trial, to determine the efficacy of 16 weeks of sildenafil therapy on exercise capacity (six-minute walk distance).

Secondary Objectives:

1. To determine the efficacy of 16 weeks of sildenafil therapy on echocardiographic estimates of right ventricular systolic pressure, and symptoms in patients with sickle cell disease and pulmonary hypertension, defined by tricuspid regurgitant velocity (TRV) ≥ 2.7 m/sec
2. Via a right heart catheterization in subjects with more severe pulmonary hypertension (TRV ≥ 3.0 m/sec stratum), to evaluate and compare the acute hemodynamic effects of inhaled nitric oxide and of oral sildenafil at rest in the catheterization laboratory and to determine the changes in hemodynamics after 16 weeks of sildenafil therapy
3. To determine the safety of 16 weeks of sildenafil therapy via adverse event reports and laboratory assessments
4. To evaluate prospective clinical outcomes in the subjects participating in the Observational Follow-up Study to the extent possible by each participating site
5. To provide subjects with open-label sildenafil for up to one year after completion of the Main Interventional Trial and to evaluate the long term safety of sildenafil in this population

Statement of Primary Efficacy Hypothesis and Primary Analysis:

The primary efficacy hypothesis is that 16 weeks of sildenafil therapy provides greater improvement in six-minute walk (6MW) distance than does placebo in patients with sickle cell disease (SCD) and pulmonary hypertension.

The primary efficacy analysis is an Analysis of Covariance Analysis (ANCOVA) on 6MW distance change from baseline to Week 16 on the Intent to Treat (ITT) Population. The primary hypothesis test will be based on a test that the average change differs between the two treatment groups, with baseline 6MW distance and TRV stratum used as covariates. This type of model controls for any impact of baseline 6MW on the treatment effect without assumptions about the slope of the relationship between the baseline and Week 16 measures.

Planned Sample Size: Up to 1000 subjects will be screened. A total of 132 subjects will be randomized into the Main Interventional Trial. Recruitment is expected to extend for approximately 13 months.

Study Design: Up to 1000 patients will be screened based on medical history, physical examination, laboratory testing, transthoracic Doppler-echocardiography, and 6MW test. All consented subjects in this

cohort will provide plasma and serum for a biomarker and DNA repository and will be followed prospectively in the Observational Follow-up Study.

Subjects found to have a screening TRV of $\geq$ 2.7 m/s will be invited to participate in the Main Interventional Trial. Upon repeat echocardiogram at baseline, subjects with TRV $\geq$ 2.7 m/s who meet all inclusion/exclusion criteria will be enrolled in the 16 week, randomized, double-blind, placebo-controlled trial of sildenafil versus placebo. The study will randomize 132 subjects in the double-blind phase of the MIT. Subjects will be stratified and randomized based on site and TRV. The primary endpoint is the change in 6MW distance across this study phase. Secondary endpoints include non-invasive estimation of pulmonary artery systolic pressure by Doppler-echocardiography, plasma NT-BNP levels, cardiovascular and sickle cell related symptoms and events, and quality of life scores. Study assessments will occur at weeks 6, 10, and 16 or early withdrawal. One-half of the subjects, those with TRVs $\geq$ 3.0 m/s, will also be evaluated with right heart catheterization (RHC) before and after 16 weeks of the intervention.

Subjects who complete the double-blind phase will be eligible to participate in the Open-label Follow-up Phase and will be treated with sildenafil for up to 1 additional year. Adverse event data will be collected every 1-3 months during this open-label phase.

Diagnosis and Key Patient Selection Criteria:

Screening Phase

Males or females 12 years of age or older with a diagnosis of sickle cell disease (documentation of sickle cell disease, including but not limited to, SS, SC, SD, or Sβ°/+ thalassemia phenotype is required).

Double-blind Phase of Main Interventional Trial

Qualification for screening phase, electrophoretic documentation of sickle cell disease, at least mild pulmonary hypertension with TRV $\geq$ 2.7 m/s by echocardiogram, and 6MW distance of 150-500 m.

Open-label Follow-up Phase of Main Interventional Trial

Completion of Main Interventional Trial.

Observational Follow-up Study

Qualification for screening phase, provision of informed consent, and a) disqualification for Main Interventional Trial; b)discontinuation from Main Interventional Trial/Open-label phase; or c) completion of Main Interventional Trial/Open-label phase.

Treatments: Sildenafil (20, 40, 80 mg) or matching placebo during the double-blind phase of the Main Interventional Trial. Sildenafil (doses range: 20-80 mg) during Open-label Follow-up Phase.

Figure 2. walk-PHaSST Study Design

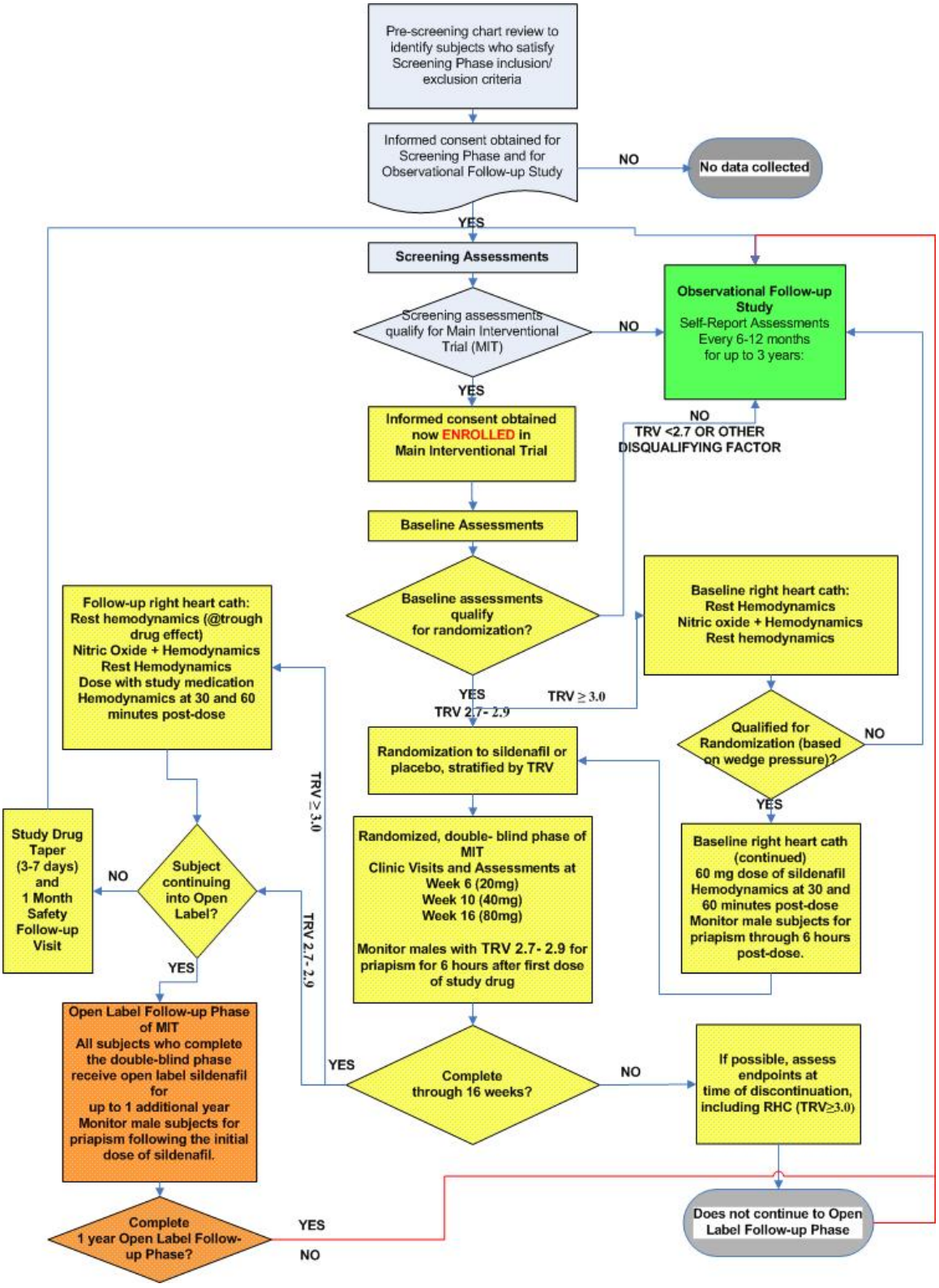

Table 3. Schedule of Events – Screening and Observational Follow-up Study

	Screening	Follow-up Study (Every 6-12 months, as possible)
Sign Informed Consent	X	
Medical history, physical examination, and vital signs (including weight)	X	
Standard laboratory tests (chemistry, CBC, urinalysis)	X	
Hemoglobin Electrophoresis	X[1]	
HIV test	X	
Echocardiogram (TRV for RV systolic function)	X	
6-minute walk test	X	
Genotype studies	X	
Pregnancy test	X	
Biomarkers (Central Labs [RBC pellets], e.g. NT-BNP)	X	
Adverse Events[2]	X	
Subject report of Hospitalizations/ED/Clinic visits		X
Subject report of Stroke / neurological events, surgical procedures, priapism, acute chest syndrome		X
Subject report of hydroxyurea therapy, pulmonary hypertension therapy, iron chelation therapy, renal replacement therapy, transfusion therapy		X

[1] Complete only for subjects who otherwise qualify for the MIT but for whom source documentation of hemoglobin electrophoresis is absent.

[2] AEs will be reported if they begin or worsen from the time a subject signs informed consent for the Screening Phase through 7 days after the last screening procedure and only if the investigator believes the event to be possibly associated with that study procedure.

Table 4. Schedule of Events – Main Interventional Study

		Randomized, Double-blind Phase			Open-Label Follow-up Phase[8]
	Baseline	6±1wk	10±1wk	16± wk / early term	
Sign Informed Consent	X				
Interim medical history, physical examination, and vital signs	X	X	X	X	
Standard laboratory tests (chemistry, CBC, urinalysis, including international normalized ration (INR) for subjects on vitamin K antagonist and activated partial thromboplastin time (aPTT) for subjects on therapeutic doses of unfractionated heparin)	X	X	X	X	
Echocardiogram (LV systolic/diastolic function)	X[1]	X		X	
Right heart catheterization – Hemodynamic parameters at rest [2]	X			X	
6-minute walk test	X[3]	X	X	X	
Borg dyspnea index	X	X	X	X	
NYHA/WHO functional class assessment	X	X	X	X	
Pregnancy test	X	X	X	X	
Ophthalmologic Exam	X[9]				
Chest X-ray [7]	X				
O_2 saturation	X	X	X	X	
Quality of Life (SF-36 or Peds-QL)	X			X	
Biomarkers (Central Labs, e.g. NT-BNP)	X	X	X	X	
Symptoms documentation: hospitalizations, ED, Clinic, transfusions, ACS, priapism	X	X	X	X	
Prior/concomitant medications & narcotics	X	X	X	X	
Compliance evaluations		X[5]	X[5]	X[5]	
Pain Questionnaire (BPI)	X	X[5]	X[5]	X[5]	
Adverse Events	X	X	X	X	X[6]

[1]Confirmatory (may be the second echo that confirms the screening echo).
[2]Only for subjects enrolled in the trial with TRV ≥ 3.0 m/s.
[3]Confirmatory (<15% change from screening 6MW test distance).
[4] Subjects will maintain a diary for 1 week between each study visit. The diary will capture study drug compliance and self-reported pain assessments.
[5]Monitoring interval every 1-3 months, based on each site's standard practice.
[6] If obtained with 3 months of signing the main study consent document, this test need not be repeated.
[7] Patients who complete the treatment phase of the MIT but who choose not to participate in the Open-Label Follow-up Study will have study drug tapered for 3-7 days and return to the clinic for a safety follow-up visit approximately 30 days after completing MIT.
[8]Required for qualifying anti-coagulated patients and for those with no available record of an exam within the past year. Ophthalmologic exams will provide baseline information for clinicians.

Table TOE
Change in Six Minute Walk Distance by Treatment Group, TRV Stratum, and Visit
Population: ITT/Safety

Visit Characteristics	Sildenafil 2.7 - 2.9 N=25	Sildenafil ≥ 3.0 N=12	Sildenafil Total N=37	Placebo 2.7 - 2.9 N=25	Placebo ≥ 3.0 N=12	Placebo Total N=37	All Treatments N=74
Screening							
Observed value							
n	25	12	37	25	12	37	74
Mean	371.2	380.2	374.1	387.6	360.7	378.8	376.5
SD	95.86	92.82	93.69	64.03	87.49	72.35	83.16
Median	394.0	389.5	394.0	408.0	373.0	390.0	390.0
Range (Min,Max)	(177,494)	(202,482)	(177,494)	(180,465)	(180,493)	(180,493)	(177,494)
Baseline							
Observed value							
n	25	12	37	25	12	37	74
Mean	389.2	364.0	381.0	393.8	371.1	386.4	383.7
SD	67.56	90.28	75.34	77.45	71.43	75.33	74.87
Median	389.0	361.0	383.0	391.0	384.5	390.0	389.5
Range (Min,Max)	(251,494)	(198,479)	(198,494)	(175,492)	(225,460)	(175,492)	(175,494)

[1] Statistics for Six Minute Walk are based on a linear mixed effects model with treatment, TRV stratum, baseline six minute walk value, time, and study site as fixed effects, and subject as a random effect using all available data from the Randomized population.
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[3] Statistics for Six Minute Walk Change from Baseline are based on a two sample Wilcoxon Rank-Sum test comparing the two treatment groups.
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Data Sources: PATIENT ENR, SIXMT
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Change in Six Minute Walk Distance by Treatment Group, TRV Stratum, and Visit
Population: ITT/Safety

Visit Characteristics	Sildenafil			Placebo			All Treatments
	2.7 - 2.9 N=25	≥ 3.0 N=12	Total N=37	2.7 - 2.9 N=25	≥ 3.0 N=12	Total N=37	N=74
Week 6							
Observed value							
n	14	11	25	15	9	24	49
Mean	369.0	375.5	371.9	438.1	411.2	428.0	399.4
SD	94.84	86.27	89.35	73.58	93.28	80.62	88.94
Median	364.0	420.0	368.0	445.0	432.0	439.5	432.0
Range (Min,Max)	(176,504)	(212,486)	(176,504)	(247,530)	(240,518)	(240,530)	(176,530)
Change from Baseline							
n	14	11	25	15	9	24	49
Mean	-17.8	10.7	-5.2	21.0	29.3	24.1	9.1
SD	59.32	48.66	55.69	65.35	32.51	54.62	56.57
Median	-1.0	7.0	5.0	6.0	23.0	12.0	7.0
Range (Min,Max)	(-142,49)	(-86,110)	(-142,110)	(-58,190)	(-4,90)	(-58,190)	(-142,190)

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Week 10							
Observed value							
n	11	8	19	8	8	16	35
Mean	364.6	386.4	373.8	460.0	385.5	422.8	396.2
SD	95.95	73.08	85.52	59.04	87.63	81.79	86.23
Median	360.0	392.5	366.0	474.5	391.0	432.5	419.0
Range (Min,Max)	(180,485)	(245,468)	(180,485)	(338,539)	(248,532)	(248,539)	(180,539)
Change from Baseline							
n	11	8	19	8	8	16	35
Mean	-22.5	11.0	-8.4	23.0	9.1	16.1	2.8
SD	60.68	71.09	65.58	60.55	36.84	48.95	59.05
Median	-21.0	9.0	4.0	-0.5	7.5	-0.5	4.0
Range (Min,Max)	(-120,89)	(-115,147)	(-120,147)	(-53,105)	(-38,78)	(-53,105)	(-120,147)

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Week 16							
Observed value							
n	10	5	15	7	7	14	29
Mean	380.7	330.2	363.9	462.4	357.0	409.7	386.0
SD	106.24	90.59	101.03	81.59	104.22	105.26	103.88
Median	390.0	363.0	363.0	479.0	374.0	431.0	407.0
Range (Min,Max)	(227,515)	(190,407)	(190,515)	(306,564)	(205,500)	(205,564)	(190,564)
Change from Baseline							
n	10	5	15	7	7	14	29
Mean	-10.5	-18.2	-13.1	27.0	-7.4	9.8	-2.0
SD	91.29	99.90	90.68	62.36	56.63	59.95	76.91
Median	24.5	-27.0	22.0	45.0	4.0	9.5	15.0
Range (Min,Max)	(-206,115)	(-170,94)	(-206,115)	(-85,90)	(-119,46)	(-119,90)	(-206,115)
Repeated Measures ANCOVA Model							
LS Means (SE) [1]			397.6 (16.21)			423.5 (14.38)	
Difference (Sildenafil-Placebo)							-26.0
95% CI							(-62.4,10.5)
P-value							0.159

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Imputed Last Visit							
Imputed value							
n	25	12	37	25	12	37	74
Mean	372.5	336.9	360.9	392.6	338.4	375.0	368.0
SD	108.66	89.05	102.85	113.93	135.79	122.27	112.42
Median	399.0	363.0	388.0	435.0	359.5	408.0	396.0
Range (Min,Max)	(176,515)	(190,459)	(176,515)	(130,564)	(0,500)	(0,564)	(0,564)
Change from Baseline							
n	25	12	37	25	12	37	74
Mean	-16.7	-27.1	-20.1	-1.2	-32.7	-11.4	-15.7
SD	99.09	100.63	98.30	81.27	121.90	95.74	96.46
Median	0.0	-12.0	0.0	2.0	-1.0	2.0	0.5
Range (Min,Max)	(-214,192)	(-272,94)	(-272,192)	(-260,170)	(-385,78)	(-385,170)	(-385,192)
Primary Analysis: ANCOVA Model							
LS Mean (SE) [2]			-15.6 (20.02)			-6.6 (19.50)	
Difference (Sildenafil-Placebo)							-9.0
95% CI							(-56.1,38.1)
P-value							0.703
Wilcoxon rank-sum test							
P-value [3]							0.726

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	Sildenafil			Placebo			All
Visit Characteristics	2.7 - 2.9 N=25	≥ 3.0 N=12	Total N=37	2.7 - 2.9 N=25	≥ 3.0 N=12	Total N=37	Treatments N=74
Imputed Last Visit							
Change from Baseline							
ANOVA Model							
LS Mean (SE) [4]			-23.8 (16.53)			-15.1 (16.53)	
Difference (Sildenafil-Placebo)							-8.7
95% CI							(-53.7,36.4)
P-value							0.702

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