Supplemental Materials

Supplementary Table 1: Adverse events reported during the REVERSE-DBMD trial. All randomized subjects were included in the adverse event analysis. Any new symptom was classified as an adverse event, regardless of whether it was believed to be related to the study drug. Asymptomatic abnormalities in laboratory tests and vital signs were defined as adverse events if they were not present at baseline and occurred on 2 or more consecutive visits during the study period. The total person-time was divided into 4 exposure categories: placebo (blinded), first 6 months on sildenafil (blinded), first 6 months on sildenafil after 6 months of placebo (open-label), and second 6 months on sildenafil (open-label). Adverse event rates (number of events per person-month) were calculated for each exposure category. Although rates are similar between groups, there were more severe adverse events (resulting in hospitalization or an emergency room visit) in subjects taking sildenafil. It is also notable that there were more occurrences of asymptomatic hypotension in the group treated with sildenafil, none of which resulted in symptoms of circulatory insufficiency.

	Placebo (blinded)	**1st six months on sildenafil (blinded)**	**1st six months on sildenafil (open-label)**	**2nd six months on sildenafil (open label)**
Number of individuals	10	10	8	7
Number of person-months	51	57	48	39
Severe AE (requiring hospitalization or ER visit)				
Death from heart failure	0	1 (10%)	0	0
Dehydration	0	0	1 (13%)	0
Pneumonia	0	0	1 (13%)	0
Prostate/scrotal infection	0	0	1 (13%)	1 (14%)
Fecal impaction	1 (10%)	0	0	0
Gastroparesis	0	1 (10%)	0	0
Adverse events				
Constitutional				
Low-grade fever	1 (10%)	0	1 (13%)	0
Fatigue	1 (10%)	0	1 (13%)	0
Weight loss	0	0	1 (13%)	0
Flu-like symptoms	1 (10%)	1 (10%)	0	1 (14%)
Coldness	0	1 (10%)	0	0
Warmth	0	1 (10%)	0	0
Flushing**	1 (10%)	1 (10%)	0	0
Insomnia**	1 (10%)	0	0	0
Cardiac/circulatory				
LVESV increase >10%	1 (10%)	2 (20%)	3 (38%)	2 (29%)
Palpitations/tachycardia	3 (30%)	2 (20%)	2 (25%)	2 (29%)
Low blood pressure*	1 (10%)	4 (40%)	3 (38%)	1 (14%)
High blood pressure	0	0	1 (13%)	0

Edema	0	1 (10%)	0	3 (43%)
Chest tightness	1 (10%)	0	0	0
Respiratory				
Cough	1 (10%)	0	1 (13%)	1 (14%)
Tachypnea	1 (10%)	0	0	0
Congestion**	1 (10%)	0	1 (13%)	0
Upper respiratory/sinus infection**	1 (10%)	1 (10%)	0	0
Gastrointestinal				
Constipation	0	0	1 (13%)	0
GI viral symptoms	0	1 (10%)	1 (13%)	1 (14%)
Nausea/vomiting*	2 (20%)	0	0	0
Diarrhea*	2 (20%)	0	0	0
Gallstones	0	0	0	1 (14%)
Genitourinary				
UTI	0	0	1 (13%)	0
Nephrolithiasis	0	0	0	1 (14%)
Frequent erections	0	1 (10%)	1 (13%)	0
Neurologic				
Headache**	2 (20%)	1 (10%)	0	0
Tingling*	0	2 (20%)	0	0
Dizziness*	0	1 (10%)	0	0
Other				
Increased intraocular pressure	0	0	1 (13%)	0
Ear pain, hearing loss*	1 (10%)	0	0	0
Depression	0	0	1 (13%)	0
Traumatic fracture	0	0	1 (13%)	0
Sensitivity to sun	0	0	1 (13%)	0
Hematologic laboratory abnormalities				
↓ hemoglobin/hematocrit	1 (10%)	1 (10%)	1 (13%)	2 (29%)
↑ hemoglobin	1 (10%)	1 (10%)	1 (13%)	1 (14%)
↓ platelets	0	0	1 (13%)	0
↑ platelets	1 (10%)	1 (10%)	1 (13%)	1 (14%)
↓ mean platelet volume	0	1 (10%)	0	1 (14%)
↓ eosinophils	0	1 (10%)	0	1 (14%)
↑ eosinophils	1 (10%)	0	0	0
↑ monocytes	1 (10%)	1 (10%)	1 (13%)	1 (14%)
↓ lymphocytes	0	2 (20%)	0	1 (14%)
↑ lymphocytes	0	1 (10%)	0	1 (14%)
Metabolic laboratory abnormalities				
↓ sodium	1 (10%)	1 (10%)	1 (13%)	0
↓ chloride	1 (10%)	1 (10%)	1 (13%)	0
↓ bicarbonate	2 (20%)	1 (10%)	2 (25%)	0
↑ anion gap	1 (10%)	2 (20%)	1 (13%)	0

↑ phosphorus	2 (20%)	1 (10%)	1 (13%)	0
↓ phosphorus	0	0	0	1 (14%)
↓ glucose	0	1 (10%)	0	0
↓ alkaline phosphatase	1 (10%)	0	1 (13%)	0
Total number of events	**36**	**38**	**37**	**22**
Number of events per person-month	**0.71**	**0.67**	**0.77**	**0.56**

**common AE's associated with sildenafil

*rare AE's associated with sildenafil

Supplementary Table 2: Genotype, phenotype, and cardiac function data for all randomized subjects.

Subject ID	Treatment group	Baseline LVESV	6 month LVESV	12 month LVESV	Age at enrollment	Diagnosis	Dystrophin mutation
1	Sildenafil	95.59	95.99	93.99	23	Duchenne	muscle biopsy diagnosis
3	Sildenafil	60.06	54.73	36.6	42	Duchenne	deletion exons 49-52
5	Sildenafil	49.49	50.6	48.3	19	Duchenne	deletion exons 3-19
7	Sildenafil	131.64	162.65	189.5	18	Duchenne	deletion exons 48-50
10	Sildenafil	127.51	deceased		26	Duchenne	large deletion, exons unknown
11	Sildenafil	232.38	270.51	307.83	21	Duchenne	c.2613_2614ins335
12	Sildenafil	78.01	81.84	74.19	27	Duchenne	deletion exons 45-52
17	Sildenafil	105.24	72.48	83.99	38	Becker	duplication exons 2-7
20	Sildenafil	65.91	withdrew		20	Duchenne	muscle biopsy diagnosis
22	Sildenafil	68.8	study closed		21	Duchenne	deletion exons 47-48
2	Placebo	115.51	107.68	111.52	20	Duchenne	muscle biopsy diagnosis
4	Placebo	61.59	58.52	62.65	24	Duchenne	large deletion, exons unknown
6	Placebo	61.27	65.34	65.68	18	Duchenne	deletion exons 46-51
8	Placebo	71.14	80.42	72.94	21	Duchenne	deletion exons 16-19
9	Placebo	84.06	86.4	82.03	24	Duchenne	deletion exons 8-9
15	Placebo	121.69	119.87	142.88	26	Becker	deletion exons 45, 47, 48
16	Placebo	123.92	118.2	133.25	21	Duchenne	c.5378_5379del
18	Placebo	35.07	36.29	study closed	33	Duchenne	muscle biopsy diagnosis
21	Placebo	123	withdrew		19	Duchenne	deletion exons 8-47
23	Placebo	71.38	study closed		20	Duchenne	deletion exons 9-18

Supplementary Video Files: Four-chamber long-axis cine MRI images from a single study subject randomized to the sildenafil treatment arm. These images demonstrate significantly enlarged ventricles and atria, tricuspid valve regurgitation, and significant wall thinning in the apical portion of the heart at baseline (Video 1), which progressively worsens by the six and 12-month follow-up studies (Videos 2 and 3). A short-axis slice from the 12-month study also shows dilated ventricles and a severely reduced ejection fraction (Video 4).

Supplementary Video 1: Long-axis cine cardiac MRI – Baseline

Supplementary Video 2: Long-axis cine cardiac MRI – Six months

Supplementary Video 3: Long-axis cine cardiac MRI – 12 months

Supplementary Video 4: Short-axis cine cardiac MRI – 12 months