TEXAS MEDICAL ASSOCIATION
Physicians Caring for Texans

TexMed 2016 Quality Research Abstract

Please complete all of the following sections.

Procedure and Selection Criteria

- Applicants should demonstrate an understanding of systematic investigation through research development, testing and evaluation designed to develop or contribute to generalizable knowledge. Judges will use the scoring described in this matrix to identify projects to be presented at the conference, as well as, projects to be considered for the awards.
- These submissions should provide general information related to the one of the following categories: patient safety, patient centered care, equity, timeliness, efficiency, or effectiveness.
- Maximum points delineated with a brief explanation of the content that should be included under each section. Applicants may describe the problem and results in narrative or graphic format.

PROJECT NAME: Clinical trial of VECTTOR therapy for Duchenne Muscular Dystrophy.

Institution or Practice Name: Alan Neuromedical Technologies, LLC

Setting of Care: Med Center Therapy, 2229 Dorrington Street, Houston, Texas 77030; Vintage Park Cardiology 20207 Chasewood Park Drive, Suite 305; Houston, Texas 77070; Sleep Diagnostics of Texas; 4840 W. Panther Creek; The Woodlands, Texas 77381; Texas Instititute of Pulmonary and Sleep Medicine, 27933 Tomball Parkway, Tomball, Texas 77375

Primary Author: Charlotte Stelly-Seitz, M.D.

Secondary Author: Donald Rhodes, D.P.M., F.A.C.F.A.S.

Other Members of Project Team: Maged Amine, M. D., FACC (Vintage Park Cardiology); William David Brown, PhD (Sleep Diagnostics of Texas); Philip Pirtle, M.D. and Chris Butler, R.R.T., C.P.F.T. (Texas Institute of Pulmonary and Sleep Medicine);

Is the Primary Author, Secondary Author or Member of Project Team a TMA member (required)?

☒ Yes ☐ No

Please provide name(s): Charlotte Stelly-Seitz, M.D.; Maged Amine, M.D., FACC; Philip Pirtle M.D.

Project Category: *(Choose most appropriate category)*

☐ Patient Safety ☒ Patient Centered Care ☐ Timeliness

☐ Efficiency ☐ Effectiveness ☐ Equity

☐ **Enhanced Perioperative Recovery/Future of Surgical Care program**

For this poster session, TMA is looking for projects that demonstrate the six aspects of Quality Care as defined by the Institute of Medicine.

- Safe - avoids injuries to patients from care that is intended to help them
- Timely - reduces waits and delays for both those who receive care and those who give care

- Effective - based on scientific knowledge, extended to all likely to benefit, while avoiding underuse and overuse
- Equitable - provides consistent quality, without regard to personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status
- Efficient - avoids waste, including waste of equipment, supplies, ideas, and energy
- Patient centered - respects and responds to individual patient preferences, needs, and values, ensuring that patient values guide all clinical decisions

Quality Research

Introduction (15 points max): *Describe 1) where the work was completed; 2) what faculty/staff/patient groups were involved, and 3) sufficient background information provided to establish the significance of the problem.*

Endpoint Testing and Evaluations

Physical Evaluations, Muscle Strength, Joint Range of Motion Testing, Quality of Life including Oswestry Disability Index

Charlotte Stelly-Seitz, M.D.; Med Center Therapy, 2229 Dorrington Street, Houston, Texas 77030

Sleep Studies

William David Brown, PhD; Sleep Diagnostics of Texas; 4840 W. Panther Creek; The Woodlands, Texas 77381

Pulmonary Monitoring

Philip Pirtle, M.D. and Chris Butler, R.R.T., C.P.F.T.; Texas Instititute of Pulmonary and Sleep Medicine, 27933 Tomball Parkway, Tomball, Texas 77375

Cardiac Monitoring (Echo cardiograms)

Maged Amine, M. D., FACC; Vintage Park Cardiology 20207 Chasewood Park Drive, Suite 305; Houston, Texas 77070

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Duchenne Muscular Dystrophy (DMD) is a fatal neuromuscular disease, affecting 2 to 3 in 10,000 male births. Currently there is no curative therapy for this disease and glucocorticoids are the only medications available that slow the decline in muscle strength and function in DMD. Although exon skipping is considered one of the most promising therapeutic approaches available, there is a necessity for developing further therapeutic strategies. This double-blind, randomized, placebo-controlled clinical trial was for children with DMD who were wheelchair bound. VECTTOR therapy was designed to improve microcirculation at the cellular level throughout the body and improve overall health.

Hypothesis (15 points max): *State the pertinent research or change hypothesis. Using if/then format, describe the 1) assumption; 2) condition; and 3) prediction(s).*

If a small clinical trial of VECTTOR treatment showed efficacy, then the need for a larger, full scale clinical trial has been demonstrated. It was predicted that this trial would demonstrate the effectiveness of VECTTOR therapy for the various aspects of DMD pathology.

Previous clinical VECTTOR treatment of children with Duchenne Muscular Dystrophy (DMD) had shown positive results. Non ambulatory children with DMD were chosen for this IRB-sanctioned, double-blind, randomized, placebo controlled clinical trial because, while there is considerable time and money invested in exon skipping trials for younger children, there is very little research being performed focusing on older children with DMD.

VECTTOR therapy is designed to improve microcirculation throughout the body by increasing the production of vasoactive neuropeptides through ultra low frequency nerve electrostimulation. Therefore, it was predicted that the subjects receiving Active VECTTOR therapy would improve more than those subjects receiving Placebo VECTTOR therapy in Muscle Strength testing, joint Range of Motion testing, Oswestry Disability Index, Sleep studies, Pulmonary Function Testing,and Echocardiograms.

Methods (25 points max): *Describe the specific methods, resources, procedures, models and/or programs used to study and test the subject of the investigation. Note charts, graphs and tables here and send as addendum with abstract form.*

This double-blind, randomized, placebo controlled clinical trial, utilizing VECTTOR Therapy, for non-ambulatory children with Duchenne Muscular Dystrophy (DMD), study was approved by the ethics committee of Salus Independent Review Board, Austin, Texas. This study was listed at clinical trials.gov (NCT 01874275). Informed consent was obtained for each patient and/or parent.

All graphs are attached in the addendum.

Study Details:

A total of 5 male children were included in this double-blind, randomized, placebo-controlled study. 6 participants were originally enrolled, however, Participant #6 withdrew due to family difficulties with travel requirements associated with the study.

All participants had been previously diagnosed with Duchenne Muscular Dystrophy based upon clinical examination and creatine phosphokinase analysis. The primary end points for the study were joint range of motion and muscle strength. At the beginning of the study, the children's ages ranged from 8 to 16, with the average age of 11 years old. The participants were randomized 66.7/33.3 Active/Placebo. Utilizing independent randomization, four of the six participants were assigned to the Active group and two were assigned to the Placebo group.

Due to randomization, only 2 of the 6 participants were given Placebo treatments. It happened that the Placebo participants were among the youngest in the study. The study was originally intended for older children with DMD. However, resources for recruiting subjects were limited, and decreasing the age requirement became necessary in order to obtain enough participants.

During the first six months, 4 of the children received Active VECTTOR therapy while 2 of the children received Placebo VECTTOR Therapy. All participants received Active VECTTOR Therapy for the second six months of the study.

There were no adverse events reported during this study.

Demographics of Study Participants

Subject #	Group	D.O.B.	Steroid Use
1	Active	5/97	Never
2	Active	12/00	5 mg Prednisone/day*
3	Active	12/04	Never
4	Placebo	9/03	24 mg Deflazacort/day
5	Placebo	8/03	Never
6**	Active	1/04	15 mg Prednisone/day

*Subject #2 was taking 20 mg of Prednisone per day, on Day 0. Within the first month of the study, his parents decreased the Prednisone to 5 mg per day, without the knowledge or consent of the principal investigator. This participant continued on 5 mg of Prednisone per day for the duration of the study.

**Subject #6 withdrew from the study due to family difficulties associated with travel required for the study.

Physical Evaluations, Muscle Strength, and Joint Range of Motion Testing

Charlotte Stelly-Seitz, M.D.; Med Center Therapy, 2229 Dorrington Street, Houston, Texas 77030

At each testing interval, subjects were evaulated by the principal investigator of the study, Dr. Stelly-Seitz. Dr. Stelly-Seitz is a pediatric physiatrist who practices in the Houston area.

All muscle and joint testing was performed at the MedCenter Therapy clinic in Houston, Texas. JTech computerized testing system was utilized including Goniometry, Grip testing, Inclinometry, Muscle Testing and Joint Range of Motion testing occurred on Day 0, 30, 60, 90, 180, and repeated at 12 months to determine muscular strength and joint Range of Motion. JTech computerized testing system was chosen on the basis of reliability and accuracy. At each of the testing intervals, the testing was administered by the same technician with the same equipment to all of the participants. Inter- and intra-tester reliability of the JTech computerized testing system has been the subject of multiple studies, all of which found high ICCs (>0.93) for both inter- and intra-tester reliability.

Oswestry Disability Index was obtained.

Sleep Studies

William David Brown, PhD; Sleep Diagnostics of Texas; 4840 W. Panther Creek; The Woodlands, Texas 77381

All sleep studies were performed at Sleep Diagnostics of Texas in The Woodlands, Texas. Prior to beginning treatment, all of the participants spent two nights in the sleep unit and their sleep study examinations were performed. The second night was used as the Day 0 data.

Sleep, breathing, arousals and limb movements were scored manually according to guidelines set forth by the American Academy of Sleep Medicine. The sleep studies were repeated at 6 months and 1 year.

Pulmonary Monitoring

Philip Pirtle, M.D. and Chris Butler, R.R.T., C.P.F.T.; Texas Instititute of Pulmonary and Sleep Medicine, 27933 Tomball Parkway, Tomball, Texas 77375

Pulmonary function testing was performed at the Texas Institute of Pulmonary and Sleep Medicine in Tomball, Texas, by the same Licensed Certified Pulmonary Function Technologist utilizing the same equipment, at each testing interval. The testing was performed utilizing the Collins ”Owl Digital Plethysmography with Diffusion Pulmonary Function Testing System". The

Predicated Protocol is from authors used in the Collins "1" Table. The testing included FVC (Forced Vital Capacity), FEV1 (Volume that has been exhaled at the end of the first second of forced expiration), FEV1/VFC (The proportion of vital capacity in the first second of expiration), and FEF Max (The maximum instantaneous flow achieved during a FVC test).

Cardiac Monitoring

Maged Amine, M. D., FACC; Vintage Park Cardiology 20207 Chasewood Park Drive, Suite 305; Houston, Texas 77070

Cardiac monitoring was performed at Vintage Park Cardiology in Houston, Texas. The echo cardiogram testing included ejection fraction, left ventricle, left atrium, right ventricle, right atrium, aortic valve, mitral valve, tricuspid valve, pulmonic valve, pericardium, and aorta.

Graphs in Addendum:

Lower body and upper body muscle strength results
- Active for 6 months vs. Placebo for 6 months
- Active for 12 months vs. Placebo for 6 months then Active for 6 months

Lower body and upper body Range of Motion results
- Active for 6 months vs. Placebo for 6 months
- Active for 12 months vs. Placebo for 6 months then Active for 6 months

Sleep studies results
- Active for 6 months vs. Placebo for 6 months
- Active for 12 months vs. Placebo for 6 months then Active for 6 months

Pulmonary Function Testing results
- Active for 6 months vs. Placebo for 6 months
- Active for 12 months vs. Placebo for 6 months then Active for 6 months

Echo cardiogram results
- Active for 6 months vs. Placebo for 6 months
- Active for 12 months vs. Placebo for 6 months then Active for 6 months

Results (25 points max): *Specifically explain what was discovered, accomplished, collected and/or produced; supports hypothesis and conclusions with adequate evidence and includes quantitative data. Note charts, graphs and tables here and send as addendum with abstract form.*

All graphs are attached in the addendum. These graphs show:

Muscle strength testing

Improved Active VECTTOR treatment lower body and upper body muscle strength results for Active vs. Placebo at 6 months

Improved Active VECTTOR treatment lower body and upper body muscle strength results for Active 12 months vs. Placebo for six months then Active for 6 months

47% averaged improvement in lower extremity muscle strength testing of Active vs. Placebo at 30 days. The subjects receiving Active VECTTOR therapy had 76% improvement while those subjects receiving Placebo VECTTOR therapy had 29% improvement.

78% averaged improvement in lower extremity muscle strength testing of Active vs. Placebo at 180 days. The subjects receiving Active VECTTOR therapy had 131% improvement while those subjects receiving Placebo VECTTOR therapy had 53% improvement.

Range of Motion testing

Improved 6 month Active VECTTOR treatment lower body and upper body Range of Motion results for Active vs. Placebo at 6 months

Improved Active VECTTOR treatment lower body and upper body Range of Motion results for Active 12 months vs. Placebo for six months then Active for 6 months

Oswestry Disability Index testing

21% improved 6 month Active VECTTOR treatment Oswestry Disability Index for Active vs. Placebo at 6 months. Those children receiving Active VECTTOR treatments had an average of 29% improvement compared to 8% improvement with Placebo treatments.

Sleep Studies

93% improved Active VECTTOR treatment 6 month sleep studies results for Active vs. Placebo for Arousal Statistics Index (ASI). The subjects receiving Active VECTTOR treatment averaged ASI improvement 41% while the subjects receiving Placebo VECTTOR treatment averaged ASI worsened 52%.

48% improved Active VECTTOR treatment 6 month sleep studies results for Active vs. Placebo for Average Percentage of REM sleep. The subjects receiving Active VECTTOR treatment averaged percentage of REM sleep improved 23% while the subjects receiving Placebo VECTTOR treatment averaged percentage of REM sleep worsened 25%.

30% improved Active VECTTOR treatment 6 month sleep studies results for Active vs. Placebo for Average Percentage of Stage 3 (N3) sleep. The subjects receiving Active VECTTOR treatment averaged percentage of Stage 3 sleep improved 6% while the subjects receiving Placebo VECTTOR treatment averaged percentage of REM sleep worsened 24%.

Improved Active VECTTOR treatment sleep studies results for Active VECTTOR treatment 12 months vs. Placebo for 6 months then Active VECTTOR treatment for 6 months

Pulmonary Function Testing

Stable PFT Active VECTTOR treatment for 6 months vs. Placebo for 6 months, in spite of 48% increased REM sleep percentage.

Improved Placebo PFT vs. Active treatment for 6 months may be due decreased REM sleep %.

Stable PFT Active VECTTOR treatment for 12 months vs. Placebo for 6 months then Active VECTTOR treatment for 6 months. Slight worsening of PFT for Placebo 6 months then Active for 6 months with increased REM sleep %.

Echo cardiogram

Improved heart valves Active for 12 months vs. Placebo for 6 months then Active for 6 months. Subjects receiving Active VECTTOR treatment for 12 months had no regurgitation of mitral valve, pulmonic valve, or tricuspid valve at the end of 12 months. Subjects receiving Placebo VECTTOR treatment for 6 months and then Active VECTTOR treatment for 6 months still had regurgitation of mitral and tricuspid valves at the end of 12 months.

Ejection fraction remained normal for all participants Active for 12 months and Placebo for 6 months then Active for 6 months

Conclusions (20 points max): *Provide a succinct interpretation of the results and evaluate what the results mean to the investigation, OR evaluate the relevance or uniqueness of what was accomplished in the immediate context of the project's purpose and describe how the investigation fits within a larger field.*

This small pilot study showed that VECTTOR treatment for non-ambulatory children with Duchenne Muscular Dystrophy is safe, timely, effective, equitable, efficient, and patient centered.

The investigators recognize that the study size is very small and is, therefore, hard to show statistical significance. The intent of this study was to demonstrate the need for further investigation of VECTTOR therapy for the treatment of DMD.

As can be seen in the attached graphs, the subjects receiving Active VECTTOR therapy out performed in all testing the subjects receiving Placebo VECTTOR therapy, even though the subjects receiving the Placebo VECTTOR therapy were younger than the subjects receiving the Active VECTTOR therapy.

Muscle strength and Range of Motion Results

Studies have shown that muscle testing of children with DMD have found that there is a significant loss of strength each year after 7 ½ years old.

VECTTOR therapy is designed to increase circulation at the cellular level throughout the body by the creation of the vasoactive neuropeptides, Calcitonin gene-related Peptide and Vasoactive Intestinal Polypeptide. Since children with DMD do not have dystrophin and the dystrophin-glycan complex is responsible for increasing circulation to the muscle during exercise, their muscle do not create nitric oxide synthetase and therefore the muscles become anoxic during muscle contraction.

There were marked improvements of muscle strength and range of motion in those participants utilizing Active VECTTOR treatment, as early as 30 days of treatment and continued throughout the year. This was in spite of the Active VECTTOR treatment children being older than the Placebo children.

When either the Active group or the Active/Placebo group started receiving Active VECTTOR therapy, the Muscle strength and Range of Motion improved. With continued Active VECTTOR therapy, the Range of Motion decreased probably due to the increase muscle strength limiting the Range of Motion.

Oswestry Disability Index Results

These children in wheelchairs had severe to crippling disability due to back pain (40 to 80% disability). There was a marked improvement in the Oswestry Disability Index in those participants utilizing Active VECTTOR treatment vs. those participants utilizing placebo VECTTOR treatment at the end of 6 months. Those children receiving Active VECTTOR treatments had an average of 29% improvement compared to 8% improvement with Placebo treatments.

Sleep Studies Results

Sleep-related respiratory disturbances in patients with muscle diseases may have significant clinical implications, partially because the patients frequently die at night.

Medical research has shown that boys with DMD awakened three times more frequently than age-matched published norms and experienced sleep stage shifts twice as often as normal children. Children with DMD have significant reduction of rapid-eye movement (REM) sleep and increased stage I sleep compared to controls. It has also been demonstrated that the percentage of REM sleep of DMD patients is inversely proportional to the pulmonary function of these patients.

It is well known that interrupted sleep leads to metabolic syndrome which leads to sleep apnea which leads to diabetes. It is also well known that children with DMD have interrupted sleep and metabolic syndrome. In spite of this knowledge, glucocorticoid steroids are a “first-line” treatment for DMD. VECTTOR therapy provides a safe and effective alternative treatment for DMD.

There were marked sleep study improvements in those participants utilizing Active VECTTOR treatment as early as 6 months, which continued throughout the year. Two of the three participants utilizing Active VECTTOR treatment had no sleep apnea episodes by the end of the year-long study.

Pulmonary Function Testing

There was stable PFT Active VECTTOR treatment for 6 months vs. Placebo for 6 months and improved Placebo PFT vs. Active treatment for 6 months with decreased REM sleep %.

Stable PFT Active VECTTOR treatment for 12 months vs. Placebo for 6 months then Active VECTTOR treatment for 6 months.

There was a slight worsening of PFT for Placebo 6 months then Active for 6 months with increased REM sleep %.

Normally, increased REM sleep % decreases pulmonary function. However, the participants receiving Active VECTTOR treatment had stable Pulmonary Function Testing in spite of increased REM sleep.

Echocardiogram Testing

Progressive cardiomyopathy is a major cause of death in DMD patients.

All of the participants had normal ejection fractions throughout the study.

All of the Active VECTTOR therapy participants had no mitral, pulmonic, and tricuspid valve regurgitation by the end of the year-long study.

50% of participants (participant #5) receiving Placebo then Active VECTTOR therapy treatment had mitral valve regurgitation

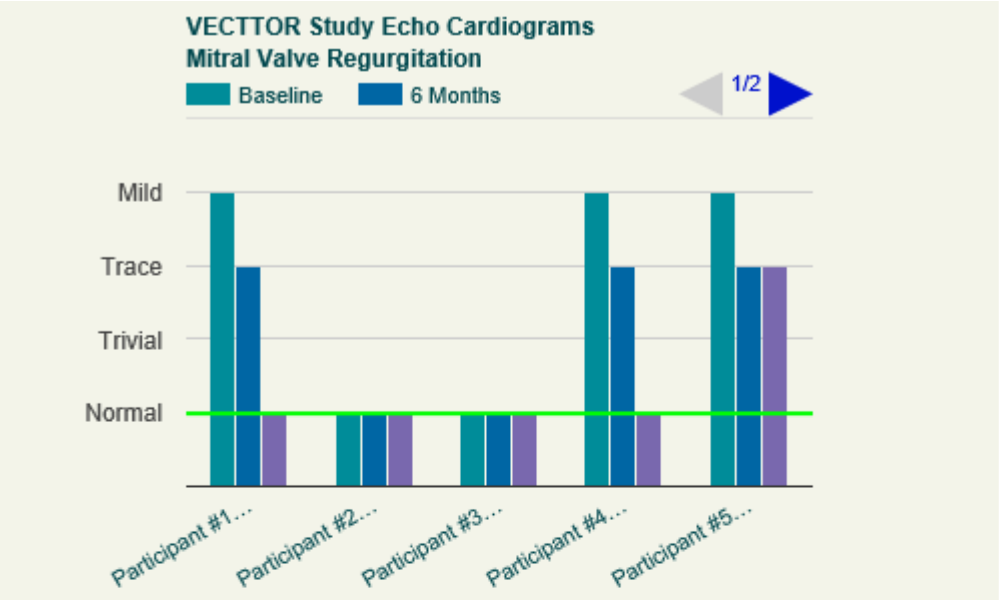
50% of participants (participant #4) receiving Placebo then Active VECTTOR therapy treatment had tricuspid valve regurgitation

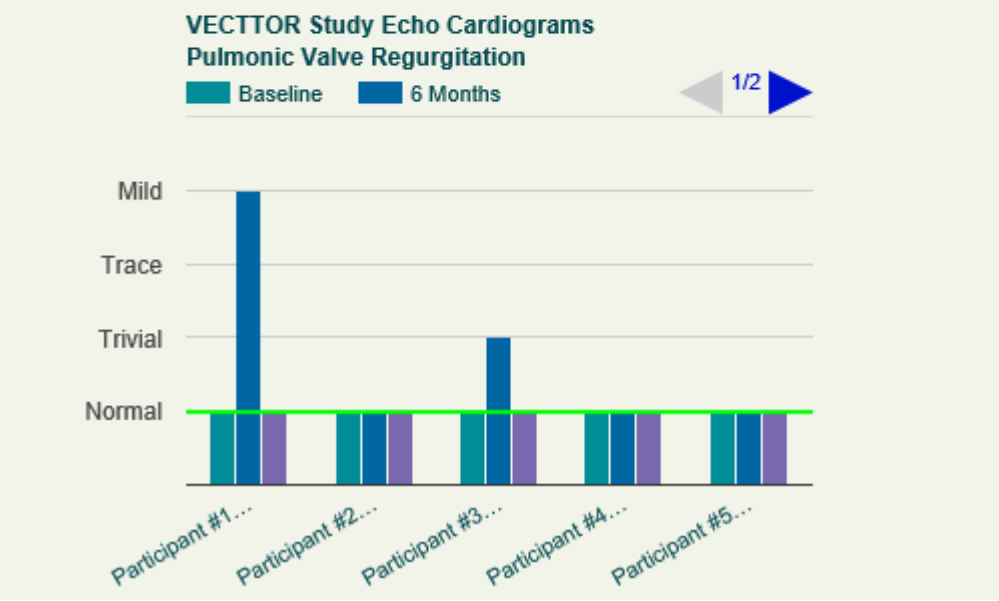
Both of the Placebo then Active VECTTOR therapy treatment participants had valve regurgitation still present at the end of the year-long study.

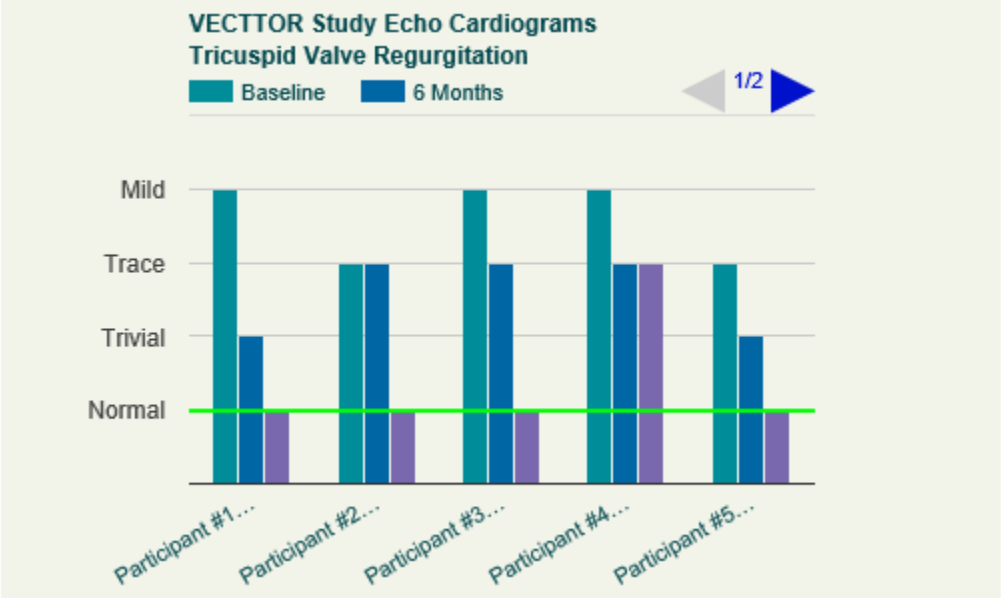
In conclusion, in this pilot study, VECTTOR therapy improved muscle strength, range of motion, back pain (as shown by improve Oswestry Disability Index), sleep studies, and cardiac function; while maintaining stable pulmonary function. A much larger double-blind, randomized, placebo-controlled clinical trial is necessary to validate these results.

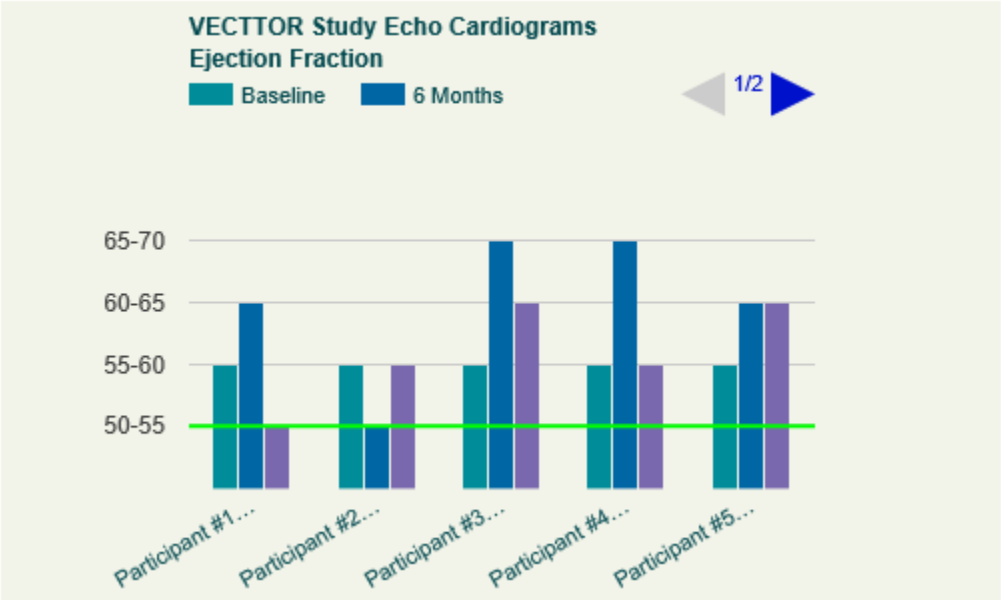
Addendum
VECTTOR clinical trial DMD Echocardiogram
1 year Results

Echo Cardiograms Day 0, Six months, and 1 year
Participants 1, 2, and 3 Active treatments for 1 year
Participants 4 and 5 Placebo treatments for 6 months, Active treatments the second 6 months
Day 0 Green
6 Months Blue
1 Year Purple

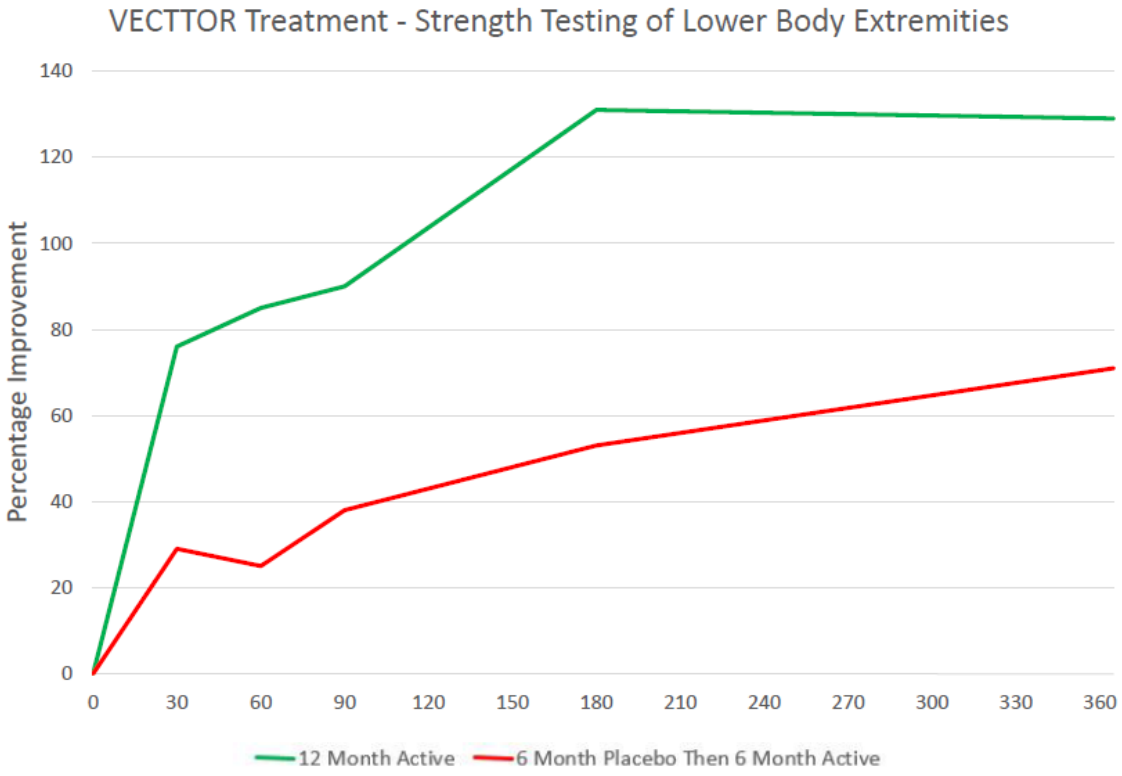


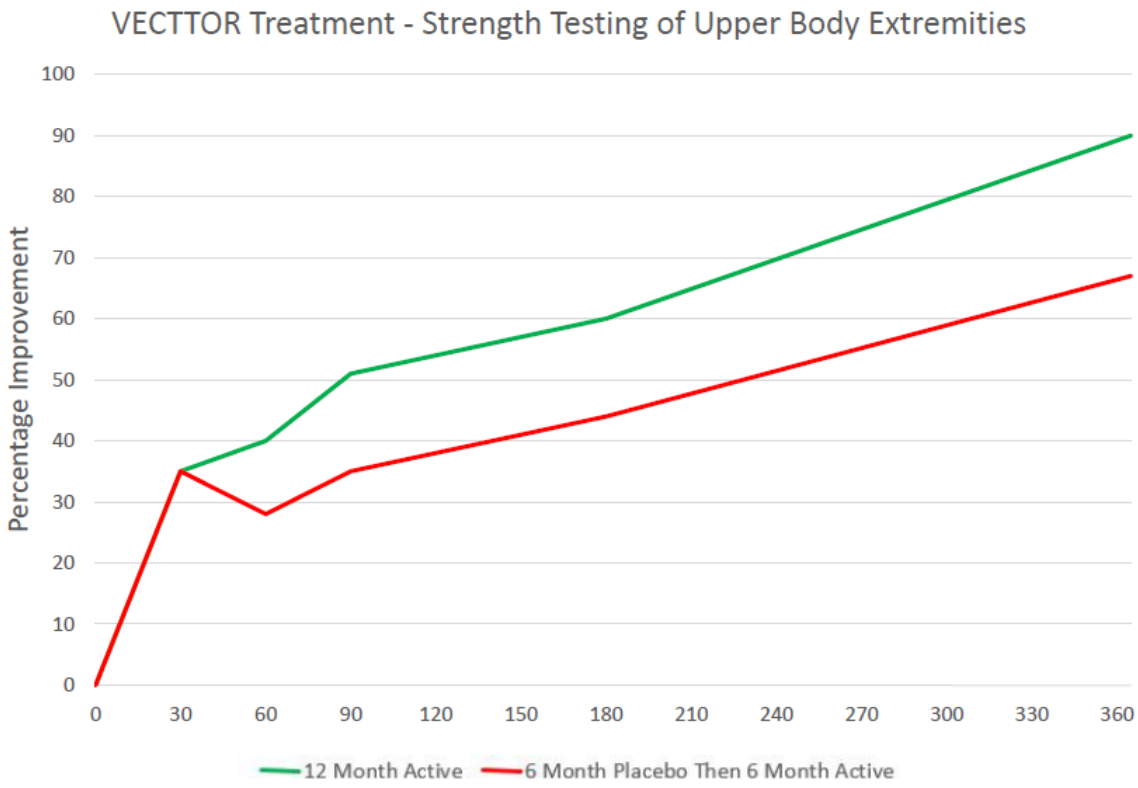


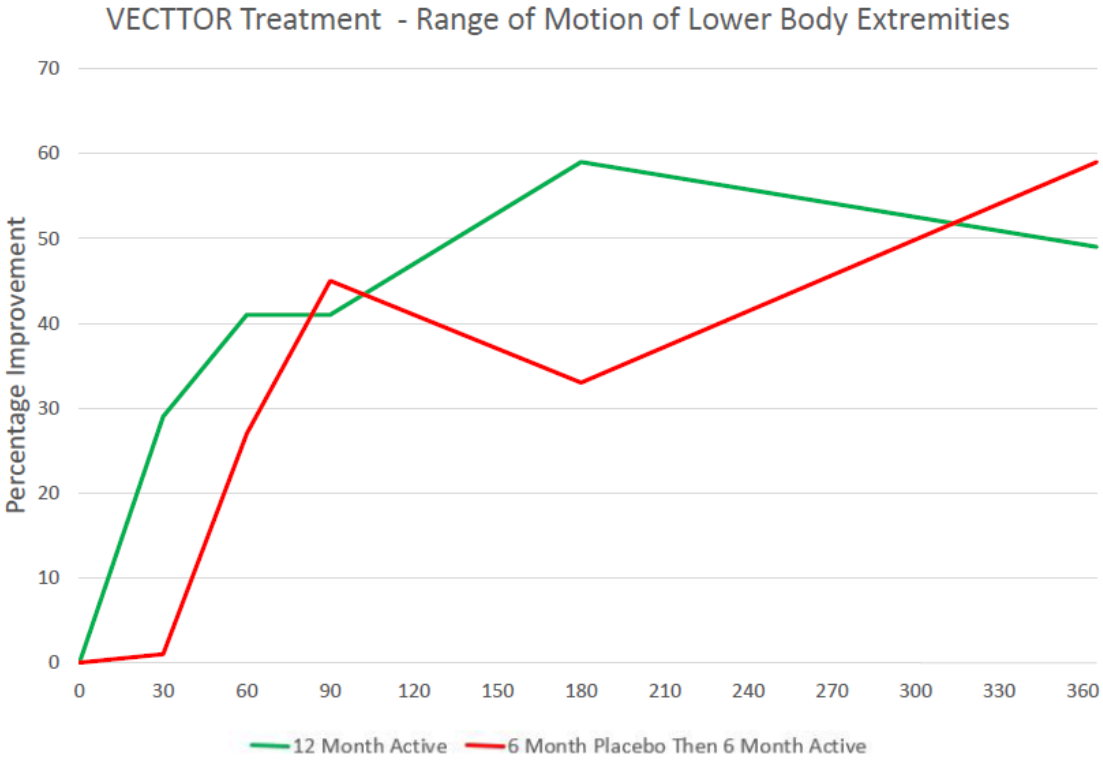

VECTTOR Study Echo Cardiograms
Tricuspid Valve Regurgitation
Baseline
6 Months
1/2
Mild
Trace
Trivial
Normal
Participant #1...
Participant #2...
Participant #3...
Participant #4...
Participant #5...

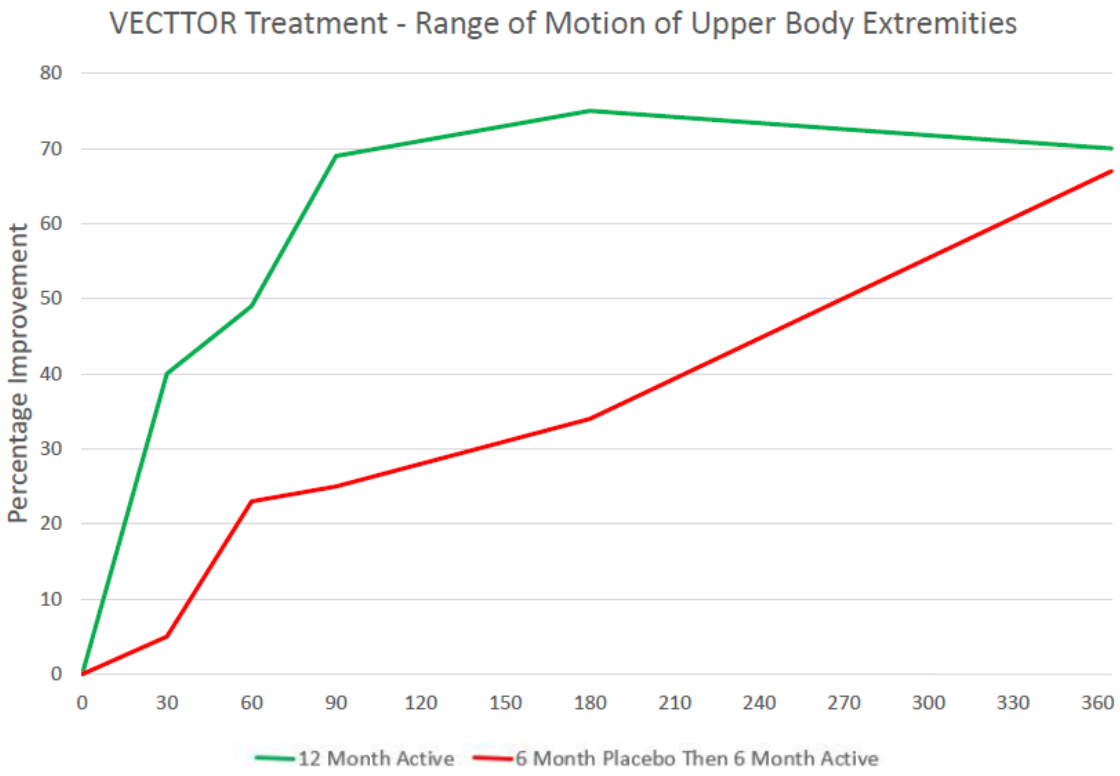

VECTTOR Study Echo Cardiograms
Ejection Fraction
Baseline
6 Months
1/2
65-70
60-65
55-60
50-55
Participant #1...
Participant #2...
Participant #3...
Participant #4...
Participant #5...

Addendum
VECTTOR clinical trial DMD Muscle Strength and Range of Motion Averaged Results

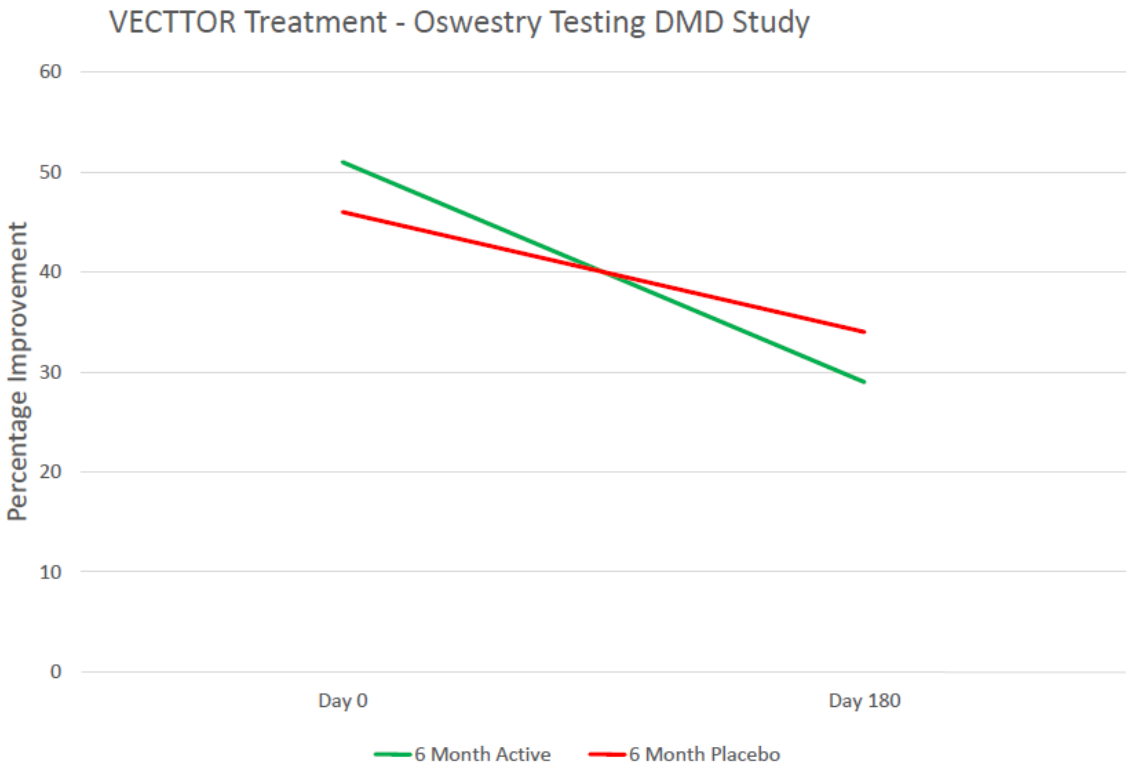



VECTTOR Treatment - Strength Testing of Upper Body Extremities
Percentage Improvement
100
90
80
70
60
50
40
30
20
10
0
0
30
60
90
120
150
180
210
240
270
300
330
360
12 Month Active
6 Month Placebo Then 6 Month Active

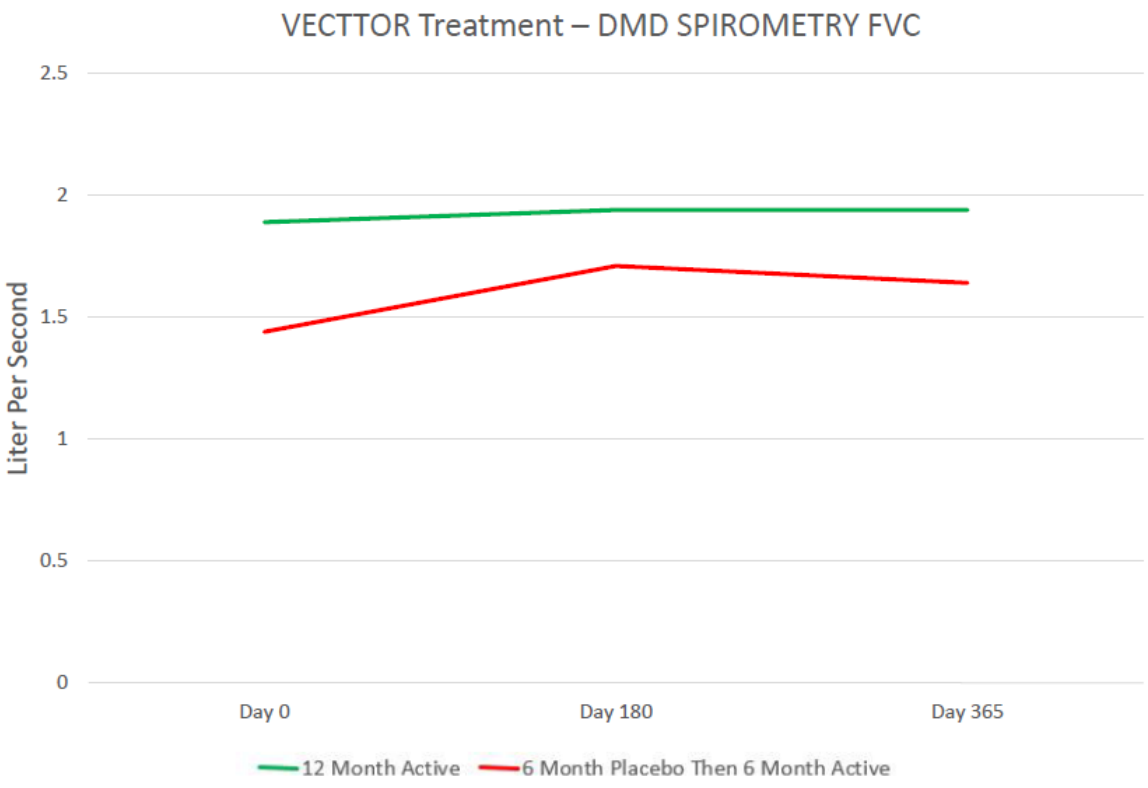

VECTTOR Treatment - Range of Motion of Lower Body Extremities
Percentage Improvement
70
60
50
40
30
20
10
0
0
30
60
90
120
150
180
210
240
270
300
330
360
12 Month Active
6 Month Placebo Then 6 Month Active

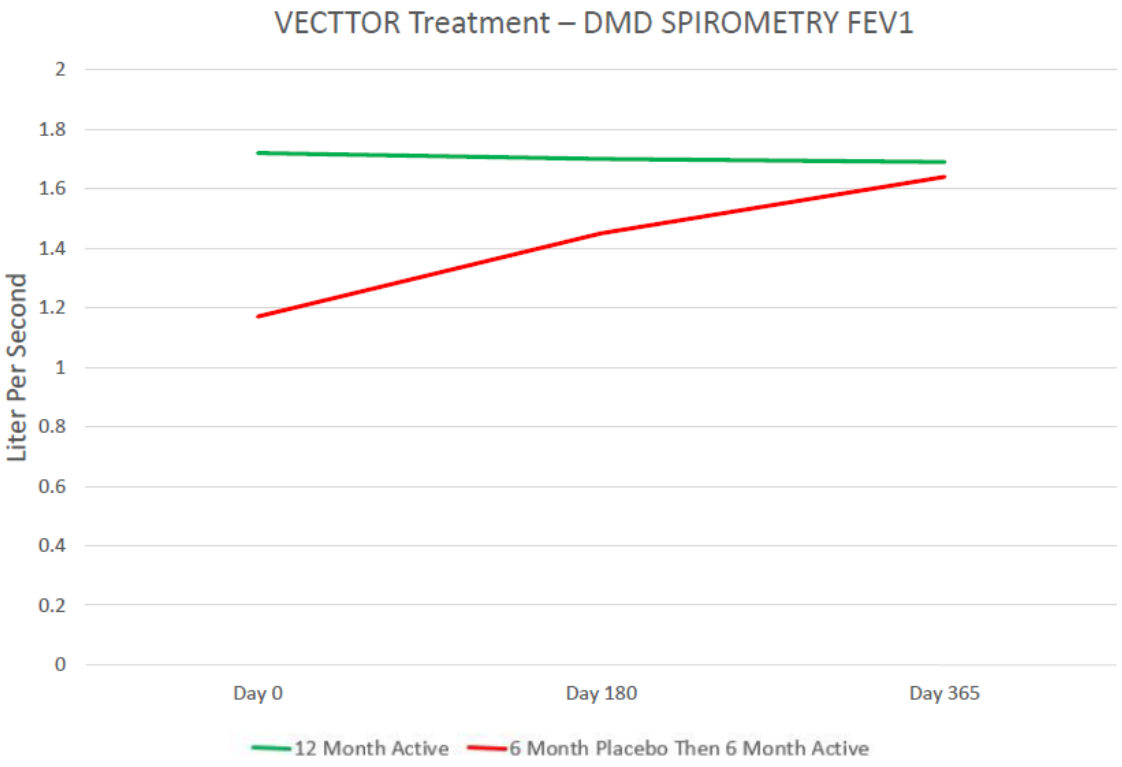

VECTTOR Treatment - Range of Motion of Upper Body Extremities
Percentage Improvement
80
70
60
50
40
30
20
10
0
0
30
60
90
120
150
180
210
240
270
300
330
360
12 Month Active
6 Month Placebo Then 6 Month Active

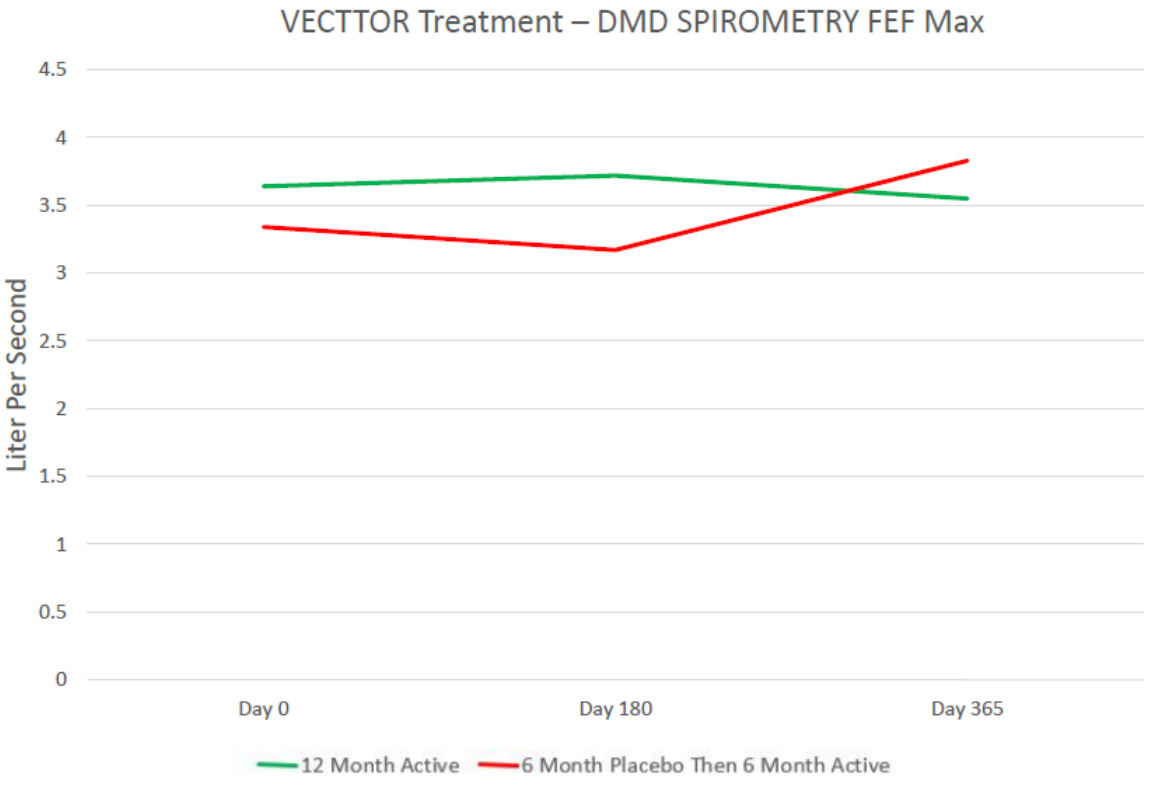
Addendum
VECTTOR clinical trial DMD Oswestry Disability Index 6month Averaged Results

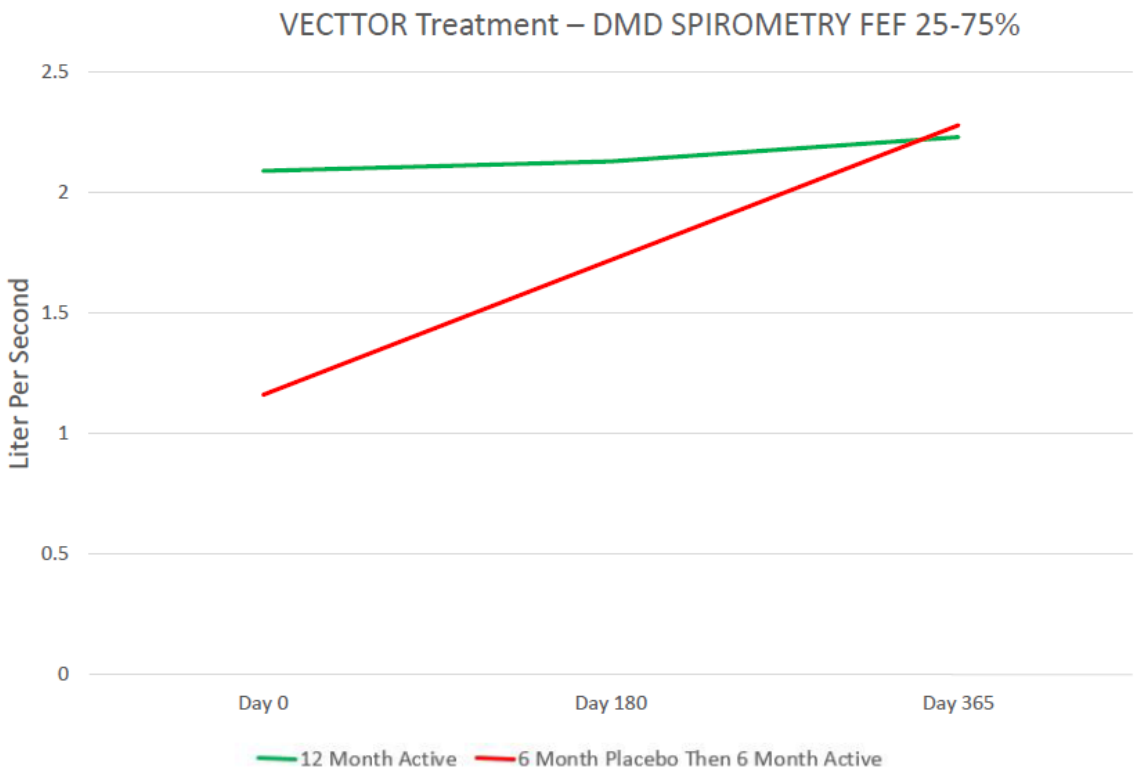


Addendum
VECTTOR clinical trial DMD Pulmonary Function Testing
1 year Averaged Results

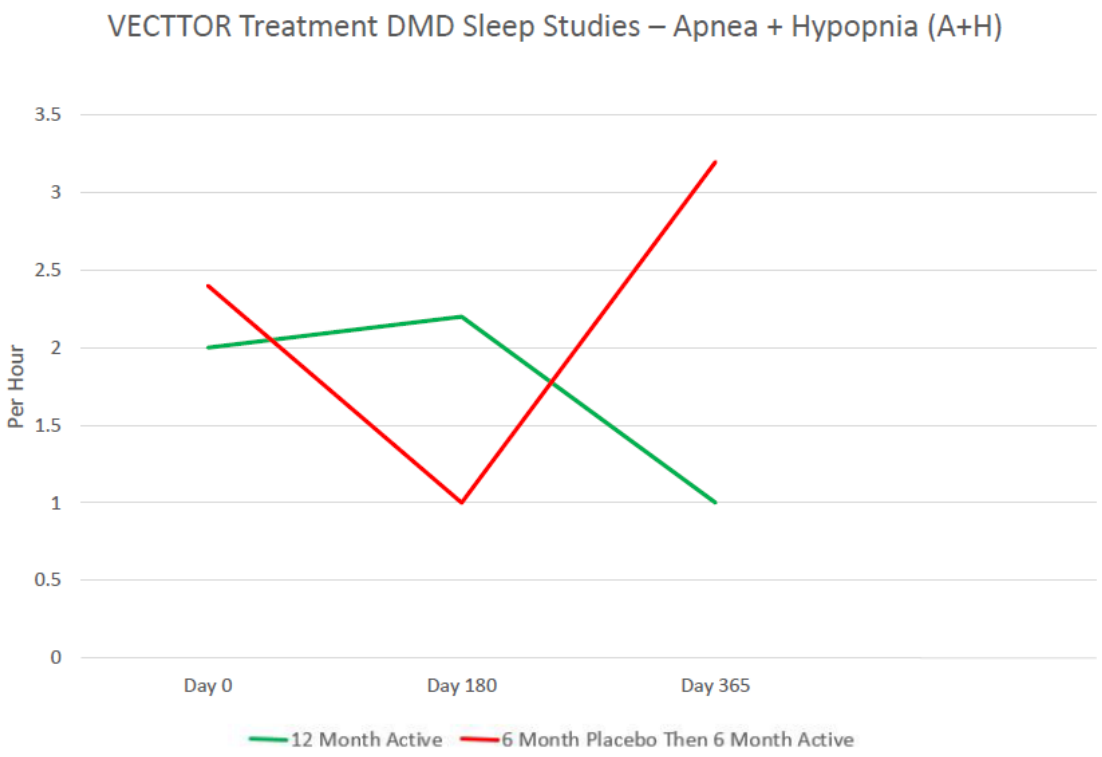



VECTTOR Treatment – DMD SPIROMETRY FEV1
Liter Per Second
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Day 0
Day 180
Day 365
12 Month Active
6 Month Placebo Then 6 Month Active


VECTTOR Treatment – DMD SPIROMETRY FEF Max
Liter Per Second
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Day 0
Day 180
Day 365
12 Month Active
6 Month Placebo Then 6 Month Active

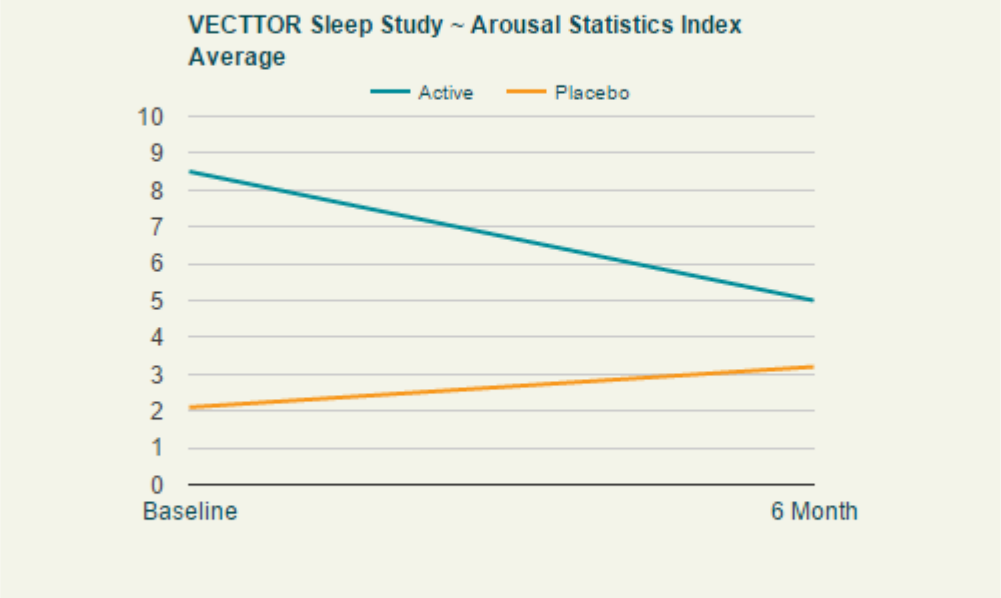

VECTTOR Treatment – DMD SPIROMETRY FEF 25-75%
Liter Per Second
2.5
2
1.5
1
0.5
0
Day 0
Day 180
Day 365
12 Month Active
6 Month Placebo Then 6 Month Active

Addendum
VECTTOR clinical trial DMD Sleep Studies
1 year Averaged Results



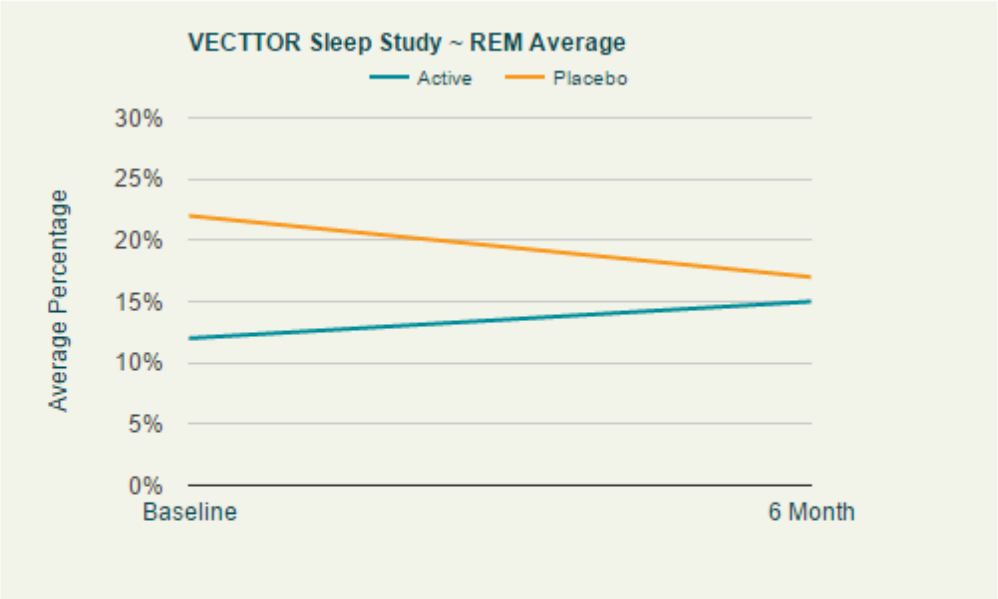
Addendum
VECTTOR clinical trial DMD Sleep Studies
6month Averaged Results

Sleep Studies
Averaged Results

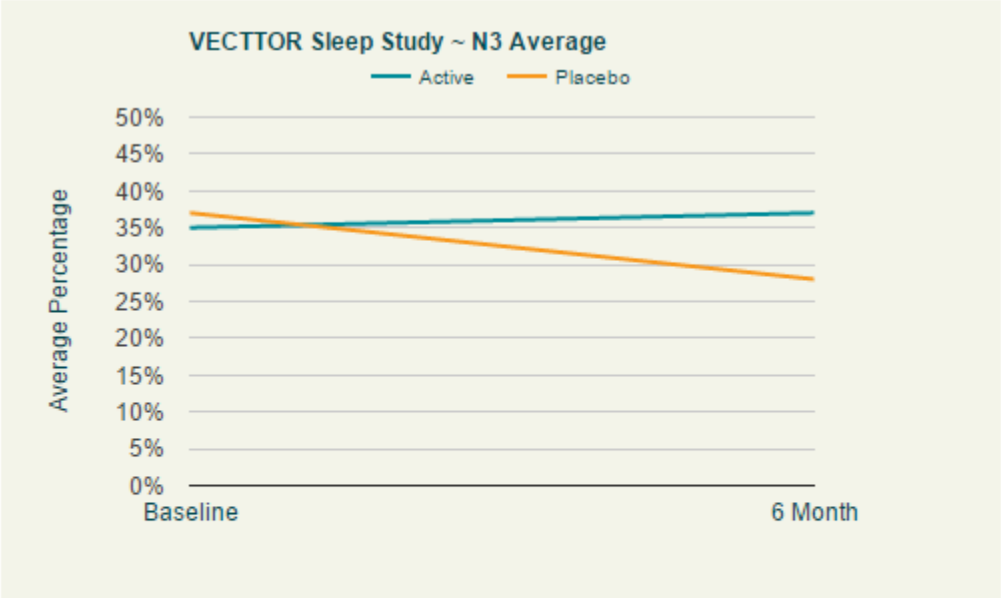


Averaged Arousal Statistics Index for those subjects receiving Active and Placebo VECTTOR treatment for six months.

The subjects receiving Active VECTTOR treatment averaged ASI improved 41% while the subjects receiving Placebo VECTTOR treatment averaged ASI worsened 52%.



Averaged percentage of REM sleep for those subjects receiving Active and Placebo VECTTOR treatment for six months - The subjects receiving Active VECTTOR treatment averaged percentage of REM sleep improved 23% while the subjects receiving Placebo VECTTOR treatment averaged percentage of REM sleep worsened 25%.



Averaged percentage of N3 Sleep (Slow Wave Sleep) for those subjects receiving Active and Placebo VECTTOR treatment for six months.

The subjects receiving Active VECTTOR treatment averaged percentage of Slow Wave Sleep improved 6%, while the subjects receiving Placebo VECTTOR treatment averaged percentage of Slow Wave Sleep worsened 24%.