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An Open-Label Trial of Recombinant Human Insulin-Like Growth Factor-I/Recombinant Human Insulin-Like Growth Factor Binding Protein-3 (rhIGF-1/rhIGFBP-3) in Myotonic Dystrophy Type 1

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Abstract

Objective—To evaluate the safety and tolerability of recombinant human insulin-like growth factor-1 (rhIGF-1) complexed with IGF binding protein-3 (rhIGF-1/rhIGFBP-3) in patients with myotonic dystrophy type 1 (DM1).

Design—Open-label dose-escalation clinical trial.

Setting—University medical center.

Participants—Fifteen moderately affected ambulatory participants with genetically-proven DM1.

Intervention—Participants received escalating dosages of subcutaneous rhIGF-1/rhIGFBP-3 over 24 weeks followed by a 16 week washout period.

Outcome Measures—Serial assessments of safety, muscle mass, muscle function, and metabolic state were performed. The primary outcome variable was the ability of participants to complete 24 weeks on rhIGF-1/rhIGFBP-3 treatment.

Results—All participants tolerated rhIGF-1/rhIGFBP-3. There were no significant changes in muscle strength or functional outcomes measures. Lean body muscle mass measured by dual energy x-ray absorptiometry increased by 1.95 kg (p=0.0007) after treatment. Participants also experienced a mean reduction in triglyceride levels of 47 mg/dL (p=0.002), a mean increase in HDL levels of 5.0 mg/dL (p=0.03), a mean reduction in HbA1c of 0.15% (p=0.03), and a mean increase in testosterone level (in men) of 203 ng/dL (p=0.002) while on rhIGF-1/rhIGFBP-3. Mild reactions at the injection site occurred (n=9 participants), as did mild transient hypoglycemia (n=3), lightheadedness (n=2), and transient papilledema (n=1).

Conclusions—rhIGF-1/rhIGFBP-3 treatment was generally well tolerated in DM1. rhIGF-1/rhIGFBP-3 was associated with increased lean body mass and improvements in metabolism, but not with increased muscle strength or function. Larger randomized controlled trials would be needed to further evaluate the efficacy and safety of this medication in patients with neuromuscular disease.

Myotonic dystrophy type 1 (DM1) is a progressive multisystem degenerative disorder caused by expansion of a CTG repeat in the dystrophia myotonica protein kinase (*DMPK*)

gene.(1) Currently there is no known treatment capable of modifying the progressive myopathy of DM1.

IGF-1 is a potent regulator of muscle differentiation and growth. This peptide hormone acts in an autocrine and paracrine fashion to promote the proliferation and differentiation of muscle precursor cells and to induce the hypertrophy of muscle fibers. IGF-1 can also enhance muscle regeneration. Forced overexpression of IGF-1 in muscle fibers can ameliorate disease in mouse models of muscular dystrophy.(2, 3)

Evidence has suggested a potential role for IGF-1 in the treatment of DM1. Previous work has shown that IGF-1 can increase the protein synthesis and differentiation competence of DM1 muscle cells in tissue culture.(4) In addition, during a small clinical study of nine patients with DM1, four months of twice daily subcutaneous rhIGF-1 resulted in improved insulin action, increased muscle protein synthesis, decreased body fat, and increased plasma testosterone.(5)

Compared to rhIGF-1 alone, the circulating half-life of rhIGF-1/rhIGFBP-3 following subcutaneous injection is extended and side effects related to peak activity, mainly hypoglycemia, may be reduced.(6) rhIGF-1/rhIGFBP-3 is currently approved for children with severe primary IGF-1 deficiency, and has been studied as a therapeutic agent for hip fractures, diabetes, and severe burns.(7–10) This two-component preparation of recombinant proteins may offer advantages for increasing the effects of rhIGF-1 on muscle while reducing peak-dose side effects. Its use for DM1 patients has not yet been described.

Here we examined the safety, tolerability, and skeletal muscle effects of rhIGF-1/rhIGFBP-3 for DM1.

METHODS

Participants

We performed a single-center, uncontrolled, dosage-escalation study of rhIGF-1/rhIGFBP-3 in 15 patients with DM1. The study was approved by the University of Rochester Institutional Review Board (Investigational New Drug number: 68,861). All study participants provided written informed consent. Participants were between 21 and 60 years-old, had genetically-confirmed DM1, could walk 30 feet without assistance (cane and leg bracing permitted), had significant distal weakness with some preservation of proximal strength, and met all pre-specified inclusion/exclusion criteria (http://clinicaltrials.gov/ct2/show/study/NCT00233519).

Treatment and Follow-up

rhIGF-1/rhIGFBP-3 (IPLEX™, mecasermin rinfabate) was provided by INSMED, Inc., Richmond, VA. Six patients were treated with 0.5 mg/kg/day rhIGF-1/rhIGFBP-3 for 8 weeks followed by 1.0 mg/kg/day for 16 weeks (Cohort 1). After review of the safety data by the Data and Safety Monitoring Board, dosage escalation was approved in the subsequent 9 participants who received 0.5 mg/kg/d for 8 weeks, 1.0 mg/kg/day for 8 weeks, and 2.0 mg/kg/day for 8 weeks (Cohort 2). After withdrawal of study medication at Week 24, all participants were followed for an additional 16 weeks.

rhIGF-1/rhIGFBP-3 was administered by participants or family members via daily subcutaneous injections at the abdomen, thigh, or deltoid regions. Dosage ranges were selected based on safety data from INSMED and previously published animal and human studies.(7–12)

Outcome Variables

The primary outcome measure was the ability of the participants to complete 24 weeks on rhIGF-1/rhIGFBP-3 treatment. All other outcomes were considered secondary for this study with no prespecified priority. Each participant had six inpatient evaluations at the University of Rochester General Clinical Research Center (Weeks 0, 8, 16, 24, 28, and 40) and nine outpatient evaluations (Weeks 2, 4, 6, 10, 12, 14, 18, 20, and 22). Serial safety monitoring included physical examinations, neuro-ophthalmic evaluations, blood counts, serum chemistries, thyroxine, thyroid stimulating hormone, gamma-glutamyltransferase, hemoglobin A1c, coagulation times, estradiol (women), testosterone (men), c-peptide, insulin, lipid profiles, urinalysis, and ECGs. Ultrasounds of the abdomen and pelvis, chest and neck x-rays, and echocardiograms were used to monitor for organomegaly or adenopathy. Serial glucose testing (4 times a day) was obtained by fingerstick glucometer for ten days following all increases in medication. Fasting glucose levels were obtained every two weeks throughout the study. Serial free and total IGF-1 levels were drawn in the morning before rhIGF-1/IGFBP-3 injections. Total IGF-1 was measured at Esoterix (Esoterix Laboratories, Calabsas Hills, CA), while analysis of free IGF-1 was performed at INSMED Therapeutic Proteins using the commercially available ELISA kits from Diagnostic Systems Laboratory (DSL, Inc.).

Strength was evaluated by quantitative muscle assessment (QMA) with a fixed dynamometer system on 12 muscle groups (six on each side for the following: elbow flexion and extension, knee flexion and extension, shoulder abduction, and ankle dorsiflexion).(13) Manual muscle testing (MMT) was performed bilaterally using a modified MRC scale in a total of 26 muscle groups (shoulder abduction, elbow flexion/extension, wrist flexion/extension, hip flexion/extension/abduction, knee flexion/extension, ankle dorsiflexion/plantarflexion, and neck extension/flexion) as described by Personius et al.(13) Other evaluations of muscle function included handgrip strength testing, myotonia testing,(14–16) Purdue pegboard test,(17–18) six-minute walk test,(19) forced vital capacity, and timed functional tests (time to traverse 30 feet, time to ascend four stairs, time to descend four stairs, and time to get up from a chair).(20) Examinations were performed by two primary evaluators who documented inter-rater reliability every 6 months. Quality-of-life was measured with the Sickness Impact Profile (SIP).

Changes in skeletal muscle were evaluated by dual energy x-ray absorptiometry (DEXA). DEXA has been established as a valid method for measuring lean body mass (LBM) and has been shown to correlate well with muscle mass calculations obtained via total body potassium-40 counting.(21–22)

Cognitive and gastrointestinal testing was implemented for the final eight participants in response to early participant reports of improved clarity of thought and reduction in diarrhea frequency while on treatment. This testing included the letter-number sequencing and vocabulary subtests from the Wechsler Adult Intelligence Scale III, the National Adult Reading Test, the Selective Reminding Test, the Rey Complex Figure Test, the Stroop Color Word Test, the Beck Depression Inventory (to monitor changes in mood),(23) the Gastrointestinal Symptom Rating Scale modified for patients with irritable bowel syndrome (GSRS-IBS),(24) and the Irritable Bowel Syndrome Impact Scale (IBS-IS).(25)

The schedule for the above evaluations is provided in Supplemental Table 1.

Statistical Analysis

All statistical tests were two-tailed and were performed using a 5% significance level. Changes from baseline to each visit in laboratory test results, LBM, muscle function, quality of life, and cognitive test results were analyzed using a repeated measures analysis of

covariance model that included visit week (categorical) and the baseline value of the outcome variable as independent variables. Ninety-five percent confidence intervals for mean changes were constructed using this model. Changes from baseline to Week 24 were of primary interest. Similar analyses were performed for changes from Week 24 (the last visit on drug) to Week 40 to evaluate the effects of drug withdrawal.

RESULTS

Baseline Characteristics

Characteristics of study participants, overall and by cohort, are shown in Table 1.

Safety and Tolerability

All 15 patients successfully completed the 40 week study. Eight-nine of the ninety inpatient appointments were kept by participants. The most commonly reported adverse event was redness or pain at the injection site (n=9 participants). Transient lightheadedness occurred in two participants. One participant had transient lightheadedness on the first day of treatment with 0.5 mg/kg/day. Another participant had transient lightheadedness on the first day of treatment with 1.0 mg/kg/day. During serial glucose testing, three transient episodes of hypoglycemia (defined as a blood glucose below 60 mg/dl by glucometer) occurred in two participants at the 2.0 mg/kg/day dosage. Neither of the patients had symptoms, and hypoglycemia was corrected with oral glucose in both cases.

One participant had transient mild swelling of the fingers at Week 14 while receiving 1.0 mg/kg/day of rhIGF-1/rhIGFBP-3. Another participant had transient leg and ankle swelling at Week 11 while receiving 1.0 mg/kg/day. A male patient developed mild non-tender enlargement of his left breast during the final 5 weeks of 1.0 mg/kg/day of rhIGF-1/rhIGFBP-3 therapy. As gynecomastia can occur in DM1, the relationship to rhIGF-1/rhIGFBP-3 was uncertain. After completing the trial the participant received testosterone supplementation therapy and his gynecomastia largely resolved.

Three adverse effects were considered moderately severe, all occurring in Cohort 2. One participant, known to have gallstones prior to entering the study, had a cholecystectomy approximately 2 ½ months into the washout period (Week 33).

One participant reported palpitations during the final week of the washout period, 15 weeks following discontinuation of the study drug. She had experienced similar symptoms prior to entry in the study, but not during the active treatment interval. Her ECG at the Week 40 washout visit showed atrial flutter, as compared to ECGs during treatment which showed normal sinus rhythms. Her serial echocardiograms during and off treatment demonstrated normal cardiac function and left ventricular ejection fraction. No other participants had any clinically significant changes in their ECGs.

One participant showed mild papilledema on the last day of rhIGF-1/rhIGFBP-3 treatment at the 2.0 mg/kg/day dosage. This finding had not been present at week 8 or 16. Concurrent medications included metronidazole, rifaximin, and Align^{tm} probiotic. She had no headache or visual symptoms, and visual field testing was normal. An MRI of the head and spinal fluid analysis were normal. A fundoscopic examination four weeks after discontinuation of the study medication and the above mentioned drugs showed reduced optic nerve swelling. A fundoscopic examination sixteen weeks after stopping medications was normal.

No other safety concerns were identified in the serial laboratory profiles of the participants. Serial ultrasounds of the abdomen and pelvis and x-rays of the chest and neck did not show evidence of organomegaly.

Total and Free IGF-1 Concentrations

As previously observed in DM1, mean basal levels of total IGF-1 in our study participants were in the lower range of normal. (5) Treatment with rhIGF-1/IGFBP3 resulted in a greater than 3-fold elevation of total IGF-1 (Figure 1). Mean levels of total IGF-1 remained elevated throughout the dose escalation period. The mean concentration of free IGF-1 increased approximately 2 fold above baseline but remained within the normal range throughout the 24 weeks of therapy (Figure 2). Notably, similar levels of serum IGF-1 were observed in both cohorts at the completion of 24 weeks of treatment.

Muscle Strength and Function

There were no significant improvements in quantitative muscle assessments, manual muscle testing, functional testing (as listed in the outcomes section), sickness impact profile, or myotonia symptoms during the study (Tables 2, 3, 4).

Skeletal Muscle Mass

Lean body mass increased after the 0.5 mg/kg/day 8-week treatment interval (mean increase 0.8 kg, 95% CI: 0.3 to 1.3, p=0.003), with further increases reaching 1.95 kg (95% CI: 1.00 to 2.90, p=0.0007) at the completion of 24 weeks of treatment (Table 2, Figure 3). The mean increase in LBM after 24 weeks was slightly larger in Cohort 2 than in Cohort 1 (2.27 kg vs. 1.36 kg). During the washout period the LBM of both cohorts decreased (Figure 3).

Laboratory Test Results

Changes in several laboratory values were observed after 24 weeks of rhIGF-1/rhIGFBP-3 treatment (Table 2; Figure 4). Triglyceride levels fell an average of 47.4 mg/dL (p=0.002), HDL levels increased by an average of 5.0 mg/dL (p=0.03), mean hemoglobin A1c (HbA1c) decreased by 0.15% (p = 0.03) while mean fasting glucose levels decreased by 5.04 mg/dL (p=0.05). Mean testosterone levels (in men) also increased by 202.7 ng/dl (p=0.002) during treatment. Supplemental Table 2 provides additional baseline and post-treatment laboratory test data from this study.

Gastrointestinal Surveys and Cognitive Testing

Three patients had baseline gastrointestinal symptoms and abnormal baseline GSRS-IBS and IBS-IS measurements. The ranges of possible GSRS-IBS and IBS-IS scores were 13 to 91 and 26 to 182 respectively. In each instance a higher score indicates worse symptoms. On average, the three affected patients' GSRS-IBS scores improved by 4.17 points (range 3 to 6) while on rhIGF-1/rhIGFBP-3. These improvements persisted throughout the washout period with participants ending the study with an average improvement of 9.67 points (range 6 to 13) compared to baseline. These same three participants also experienced improvements of 21, 61, and 2 points in their IBS-IS scores while on treatment.

There were no significant adverse changes in cognition while participants were on therapy. One of seven cognitive tests showed a statistically significant improvement after 24 weeks (Rey Complex Figure Delayed Recall Score) with a mean improvement over baseline of 7.1 points (p=0.002) during treatment and a decrement of 1.6 points (p=0.20) during the washout period.

COMMENT

This is the first study to utilize a two-component preparation of recombinant proteins, rhIGF-1/rhIGFBP-3, for myotonic dystrophy. This study demonstrated that rhIGF-1/

rhIGFBP-3 given for 24 weeks in escalating dosages is well tolerated in a cohort of DM1 participants.

No patients withdrew from the study secondary to intolerable adverse events or for any other reason. All participants were able to fully comply with the 24 week medication escalation schedule. This is in direct contrast to a previous study of rhIGF-1 (without rhIGFBP-3) in patients with DM1 which had a 20% drop out rate secondary to intolerable adverse events. (5) By combining a factor with its serum binding protein, and thereby attenuating peak dose activity, the ability to deliver IGF-1 at levels that have demonstrable biologic effects on the intended target (skeletal muscle) without significant dose-limiting hypoglycemia is an important finding. Although adverse events were noted, these observations were primarily mild (and perhaps unrelated to the study medication) in a population with a severe, life-altering disease.

Reduced or low normal levels of IGF-1 occur in patients with DM1 and may be correctable via therapeutics.(5) The cause of reduced levels of IGF-1 in DM1 is not entirely clear but may relate in part to disturbances in the DM1 hypothalamo-pituitary-adrenal axis. Necrosis of muscle fibers, fibrosis of the muscle, and muscle contractures are less conspicuous in DM1 than in most other forms of dystrophy. Instead, both the synthesis and catabolism of muscle protein in these patients is slowed and the histopathology is characterized mainly by muscle fiber atrophy. (26–28) The possibility that muscle weakness and atrophy are treatable in DM1 suggests that there may be a therapeutic role for conventional endocrine therapies. There is evidence that IGF-1 improves insulin resistance, promotes protein anabolism, and enhances cell growth.(29) It is plausible that some of these effects may counter the anabolic deficiency in DM1 caused by the insulin resistance, gonadal insufficiency, and decreased growth hormone.

IGF-1 receptors are widespread throughout the human body, existing on muscle, the brain, and on the gastrointestinal tract.(30) It is reasonable to anticipate that rhIGF-1/rhIGFBP-3 may exert effects on many of its target tissues. Our findings of improvement in LBM, certain laboratory values, and possibly gastrointestinal function may indicate that the increase in IGF-1 levels observed in each patient exerted the expected physiological stimulation, enhanced insulin sensitivity, and improved muscle anabolism; however, randomized controlled trials that control for multiple comparisons are required to confirm and expand on these findings.

No statistically significant change in strength and functional testing outcomes was observed despite a ~2 kg gain in LBM. The explanation for this disparity is currently unknown. It is possible that increased muscle tissue was distributed too diffusely and for too short a time to produce a measurable impact on strength testing. A previous study of testosterone in men with DM1 showed a similar disparity, perhaps suggesting that measures of muscle mass may be more sensitive than measures of muscle strength in detecting therapeutic effects in DM1. (20) However, we cannot exclude the possibility that increased muscle mass was accompanied by a reduction of muscle contractility. Signaling through the IGF-1 receptor upregulates the expression of *DMPK* in myogenic cells (31), raising the possibility that therapeutic effects of IGF-1 in DM1 could be blunted by increased accumulation of toxic RNA. In this regard, it is noteworthy that other dystrophies, such as Duchenne and Becker muscular dystrophy, may not be subject to this same limitation.

This study had several limitations, including a small sample size and the absence of a placebo group. The results concerning the activity and efficacy measures must be interpreted with some caution due to the large number of statistical tests performed. Particularly for the evaluations of muscle strength and function, gastrointestinal symptoms, and cognition,

practice/training effects or “placebo” effects (knowledge that the participants are receiving active treatment) could be responsible for some of the findings. Additional studies will be required to determine if the observed reductions in serum glucose, HbA1c, and triglyceride levels may ultimately have extended beneficial effects on a DM1 population predisposed to both impaired glucose tolerance and lipid abnormalities

Dosages of 0.5mg/kg/day, 1.0mg/kg/day, and 2.0mg/kg/day of rhIGF-1/rhIGFBP-3 were tolerated well by participants. Due to the study design it is not possible to determine if beneficial trends have occurred due to sustained 24-week maintenance of a dosage of rhIGF-1/rhIGFBP-3 of 0.5mg/kg/day or whether there is an additional benefit related to higher dosages of 1.0 and 2.0 mg/kg/day. Future controlled parallel group trials using different dosages for extended periods of time (6–12 months) will help to clarify whether higher or relatively low dosages of rhIGF-1/rhIGFBP-3, if any, are the most effective.

In summary, this is the first study to demonstrate the feasibility of utilizing rhIGF-1/rhIGFBP-3 as a neuromuscular therapy for a muscular dystrophy. This is also one of the first evaluations of a two-component preparation of recombinant proteins for any neurological disease. The results from this trial concerning the activity markers are encouraging but require longer controlled parallel group trials to clarify the longer-term efficacy, safety, and optimal dosage of rhIGF-1/rhIGFBP-3 as a treatment for DM1 and other muscular dystrophies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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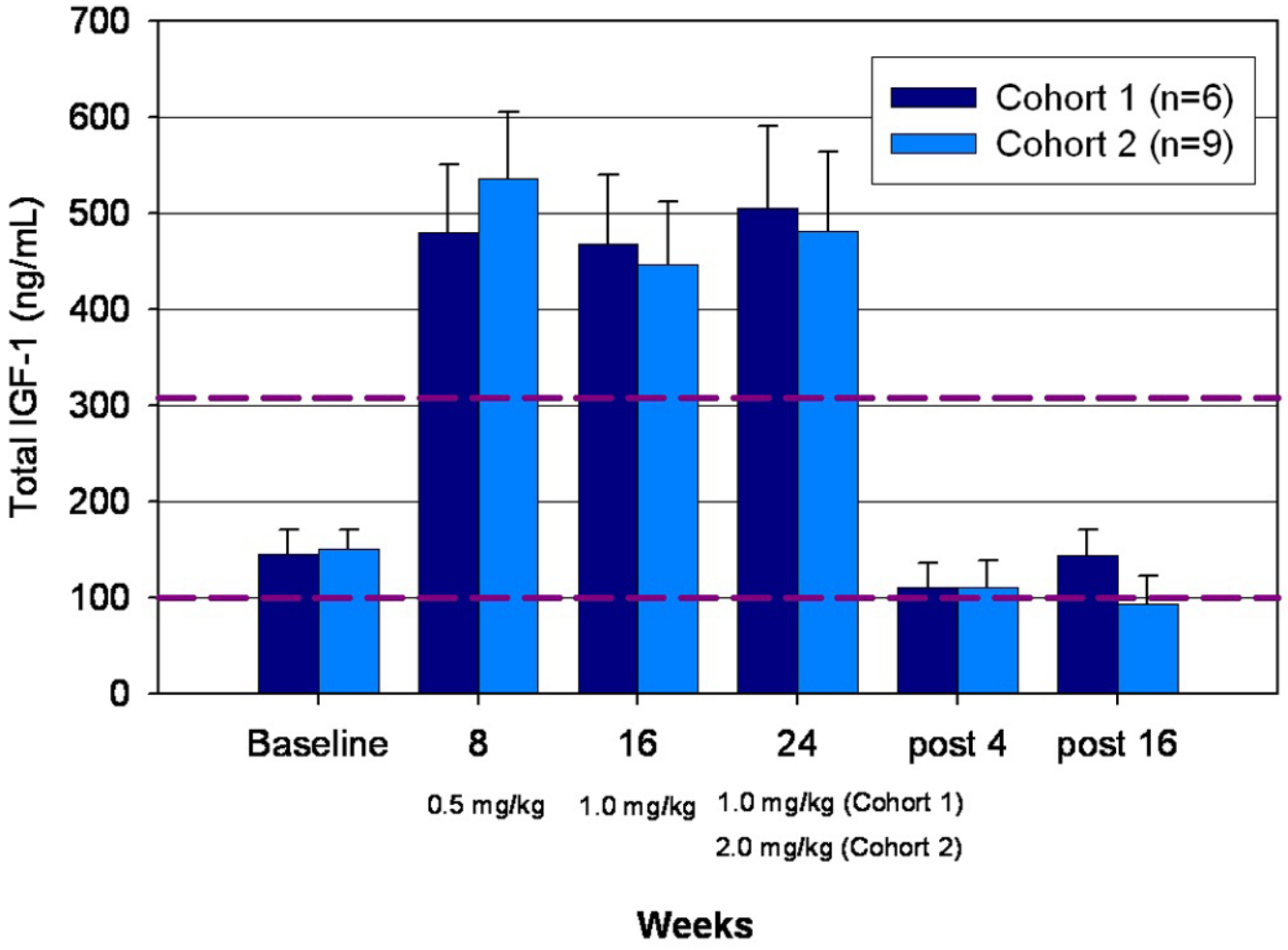

Figure 1.
Mean Total IGF-1 Levels. Normative range indicated as dashed line: 100 to 308ng/mL (Esoterix Laboratories). One participant in Cohort 1 missed their 24 week appointment. Error bars = standard error of the mean. **(attached)**

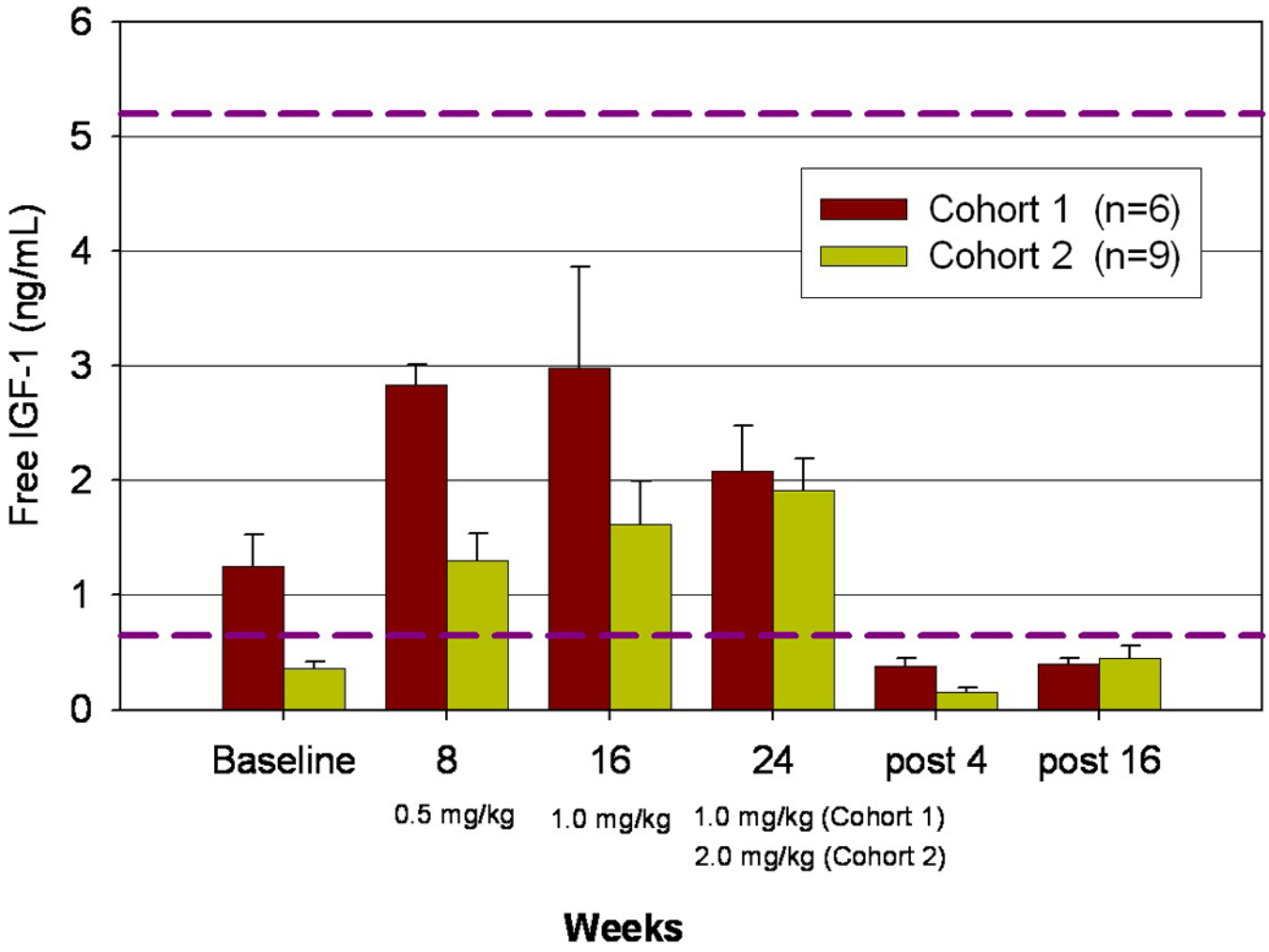

Figure 2.

Mean Free IGF-1 Levels. Normative range indicated as dashed line: 0.65 to 5.20 ng/mL.(32) One participant in Cohort 1 missed their 24 week appointment. Error bars = standard error of the mean. **(attached)**

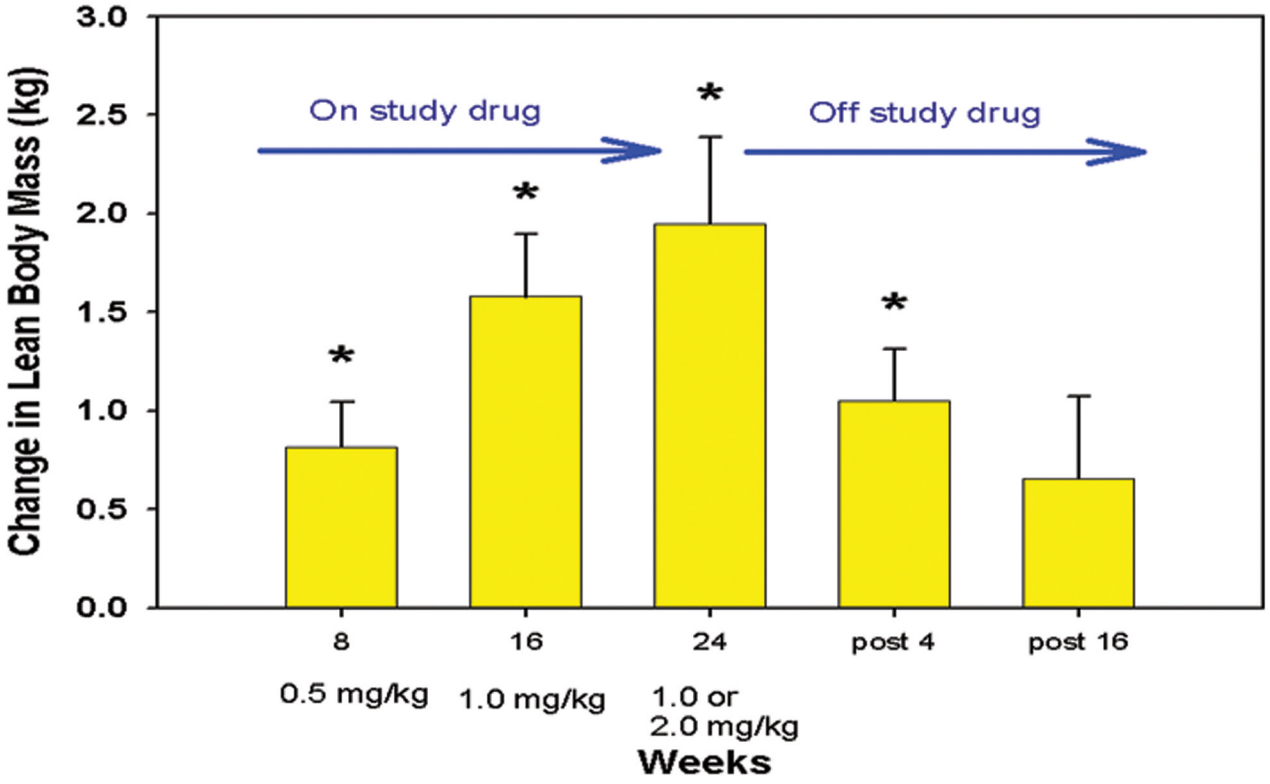

Figure 3.
Mean Changes in Lean Muscle Mass Measured by Dual Energy X-ray Absorptiometry (DEXA) for Both Cohorts: n=15 except for the 24 week visit (n= 14). * $p<0.05$ (compared to baseline). Error bars = standard error of the mean. **(attached)**

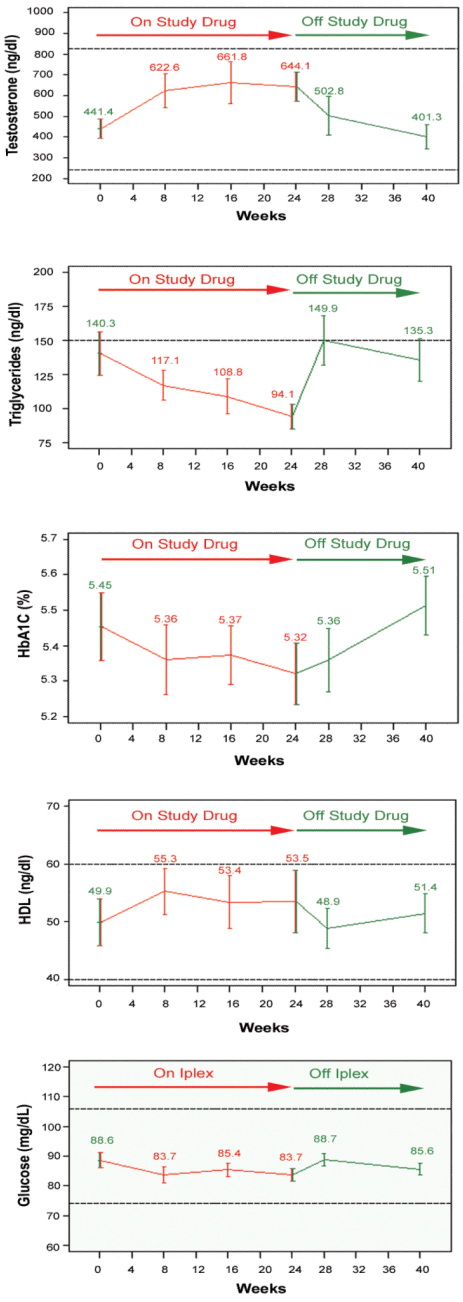

Figure 4.

Mean responses over time for testosterone, triglycerides, HbA1C, High-Density Lipoprotein (HDL), and fasting plasma glucose. Normative ranges indicated as dashed lines. Error bars = standard error of the mean. **(attached)**

Table 1

Baseline Characteristics of Study Participants

	All (n = 15)	Cohort 1 (n = 6)	Cohort 2 (n = 9)
Male Gender (%)	47%	50%	44%
Age (years)	42.7 (10.4)	49.3 (10.5)	38.4 (8.1)
Height (cm)	172.9 (8.7)	171.2 (11.2)	174.1 (6.9)
Total Body Mass (kg)	69.1 (14.1)	69.1 (12.7)	69.2 (15.7)
Lean Body Mass (kg)	43.6 (10.4)	43.8 (9.3)	43.6 (11.7)
CTG Repeat Size	355.9 (209.6)	282.3 (194.7)	405.0(215.4)
BMI (kg/m^2)	23.0 (3.9)	23.6 (4.1)	22.7 (4.0)
Total IGF-I (ng/ml)	148.7 (58.4)	145.8 (59.9)	150.6 (61.0)
Free IGF-I (ng/ml)	0.72 (0.62)	1.25 (0.68)	0.36 (0.19)
FVC (L)	3.5 (0.8)	3.6 (0.8)	3.5 (0.8)
QMA (% normal)	56.9 (16.7)	57.8 (13.5)	56.2 (19.3)
Average MMT	4.1 (0.4)	4.1 (0.4)	4.1 (0.4)
Values are mean (standard deviation)			

Legend: BMI: Body mass index; FVC: Forced vital capacity (in liters); QMA Quantitative Muscle Assessment score across all muscles tested, expressed as a percentage of the expected normal value for age, gender, and height; MMT: average Manual Muscle Testing score across all muscles tested

Table 2

Mean changes in measures of muscle mass and strength, functional testing and quality-of-life, laboratory testing, and gastrointestinal survey scores (for entire study group).

	Baseline	Treatment (Mean change from baseline to 24 weeks)		Washout (Mean change from 24 weeks to 40 weeks)		Entire Study (Mean change from baseline to 40 weeks)	
	Mean (Standard Deviation)	Mean (95% confidence interval)	n (p-value)	Mean (95% confidence interval)	n (p-value)	Mean (95% confidence interval)	n (p-value)
Muscle Mass and Strength							
DEXA Lean (kg)	43.63 (10.43)	1.95 (1.00,2.90)	14 (<0.01)	−1.28 (−1.92, −0.65)	14 (<0.01)	0.66 (−0.24,1.55)	15 (0.14)
MMT	4.09 (0.37)	0.09 (−0.10,0.29)	14 (0.32)	−0.05 (−0.20,0.10)	14 (0.50)	0.06 (−0.07,0.19)	15 (0.36)
QMA	56.85 (16.72)	−2.44 (−6.17,1.30)	14 (0.18)	0.49 (−2.85,3.82)	14 (0.76)	−2.26 (−5.82,1.29)	15 (0.19)
BMI (kg/m^2)	23.03 (3.94)	0.52 (0.09,0.96)	14 (0.02)	−0.37 (−0.69, −0.05)	14 (0.03)	0.12 (−0.38,0.62)	15 (0.61)
Functional Testing and QOL							
Hand Grip (kgf)	11.66 (6.10)	−1.09 (−2.58,0.41)	14 (0.14)	0.30 (−0.71,1.32)	14 (0.53)	−0.87 (−1.94,0.20)	15 (0.10)
FVC (L)	3.54 (0.78)	−0.04 (−0.18,0.11)	14 (0.61)	0.01 (−0.07,0.09)	14 (0.72)	−0.03 (−0.18,0.13)	15 (0.73)
Walk 30 feet (sec)	5.05 (3.00)	0.34 (−0.05,0.72)	14 (0.08)	−0.20 (−0.73,0.33)	14 (0.43)	0.17 (−0.15,0.50)	15 (0.27)
Six Minute Walk (feet)	1414.86 (444.76)	116.29 (−56.9,289.5)	7 (0.15)	−2.00 (−73.4,69.4)	7 (0.95)	114 .29 (−43.8,272.4)	7 (0.13)
Ascend (sec)	2.36 (2.30)	0.29 (0.07,0.52)	14 (0.01)	0.00 (−0.26,0.26)	14 (1.00)	0.25 (0.08,0.43)	15 (<0.01)
Descend (sec)	2.57 (3.00)	0.04 (−0.22,0.30)	14 (0.77)	−0.19 (−0.63,0.26)	14 (0.39)	−0.16 (−0.72,0.40)	15 (0.55)
Purdue Pegboard (points)	12.80 (4.31)	−0.21 (−1.72,1.29)	14 (0.76)	0.54 (0.07,1.01)	13 (0.03)	0.43 (−1.09,1.94)	14 (0.55)
SIP (%)	9.38 (4.49)	−1.21 (−3.46,1.05)	15 (0.27)	1.11 (−1.17,3.38)	15 (0.32)	−0.10 (−2.72,2.52)	15 (0.94)

	Baseline	Treatment (Mean change from baseline to 24 weeks)		Washout (Mean change from 24 weeks to 40 weeks)		Entire Study (Mean change from baseline to 40 weeks)	
	Mean (Standard Deviation)	Mean (95% confidence interval)	n (p-value)	Mean (95% confidence interval)	n (p-value)	Mean (95% confidence interval)	n (p-value)
Laboratory Tests							
HDL (mg/dL)	49.93 (15.64)	5.00 (0.70,9.30)	14 (0.03)	−2.21 (−9.47,5.04)	14 (0.52)	1.47 (−4.43,7.36)	15 (0.60)
Triglycerides (mg/dL)	140.27 (60.65)	−47.36 (−73.0,−21.7)	14 (<0.01)	36.36 (12.6,60.1)	14 (<0.01)	−4.93 (−30.8,20.9)	15 (0.69)
HbA1C (%)	5.45 (0.37)	−0.15 (−0.28,−0.02)	14 (0.03)	0.19 (0.09,0.30)	14 (<0.01)	0.06 (−0.04,0.16)	15 (0.20)
Glucose (mg/dL)	88.57 (10.12)	−5.04 (−10.02,−0.05)	14 (0.05)	2.43 (−2.08,6.93)	14 (0.27)	−2.97 (−7.61,1.67)	15 (0.19)
Testosterone (ng/dL)	441.43 (124.57)	202.71 (113.6,291.9)	7 (<0.01)	−242.67 (−638.0,152.6)	3 (0.12)	4.67 (−251.3,260.6)	3 (0.94)

Legend. DEXA Lean: Lean body mass measured by dual energy x-ray absorptiometry; MMT: average Manual Muscle Testing score across all muscles tested; QMA: Average Quantitative Muscle Assessment score across all muscles tested, expressed as a percentage of the expected normal value for age, gender, and height; FVC: Forced vital capacity; Ascend: Time to ascend 4 steps; Descend: Time to descend 4 steps; SIP: Sickness Impact Profile; HDL: High-Density Lipoprotein; HbA1C: Hemoglobin A1c level.

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Table 3

Mean changes in measures of muscle mass and strength, functional testing and quality-of-life, laboratory testing, and gastrointestinal survey scores (for N=6 Cohort 1).

	Baseline	Treatment (Mean change from baseline to 24 weeks)		Washout (Mean change from 24 weeks to 40 weeks)		Entire Study (Mean change from baseline to 40 weeks)	
	Mean (Standard Deviation)	Mean (95% confidence interval)	n (p-value)	Mean (95% confidence interval)	n (p-value)	Mean (95% confidence interval)	n (p-value)
Muscle Mass and Strength							
DEXA Lean (kg)	43.75 (9.32)	1.36 (−0.50,3.23)	5 (0.11)	−1.73 (−3.19, −0.27)	5 (0.03)	−0.22 (−1.36,0.92)	6 (0.64)
MMT	4.06 (0.35)	0.08 (−0.17,0.34)	5 (0.41)	−0.17 (−0.46,0.11)	5 (0.17)	−0.03 (−0.32,0.26)	6 (0.80)
QMA	57.80 (13.51)	−5.50 (−10.32,−0.68)	5 (0.03)	0.49 (−7.79,8.77)	5 (0.88)	−5.28 (−10.79,0.23)	6 (0.06)
BMI (kg/m^2)	23.61 (4.07)	0.30 (−0.15,0.75)	5 (0.14)	−0.48 (−0.79, −0.18)	5 (0.01)	−0.21 (−0.68,0.26)	6 (0.31)
Functional Testing and QOL							
Hand Grip (kgf)	12.52 (5.01)	−1.48 (−4.15,1.19)	5 (0.20)	1.44 (0.11,2.78)	5 (0.04)	−0.38 (−2.60,1.84)	6 (0.68)
FVC (L)	3.58 (0.83)	−0.05 (−0.35,0.25)	5 (0.67)	0.09 (−0.22,0.05)	5 (0.15)	−0.13 (−0.43,0.18)	6 (0.33)
Walk 30 feet (sec)	5.10 (1.43)	0.24 (−0.58,1.06)	5 (0.46)	0.24 (−0.48,0.96)	5 (0.41)	0.52 (0.09,0.94)	6 (0.03)
Ascend (sec)	1.87 (0.54)	0.22 (−0.11,0.55)	5 (0.14)	0.24 (−0.21,0.69)	5 (0.22)	0.33 (−0.03,0.70)	6 (0.07)
Descend (sec)	1.82 (0.38)	0.26 (−0.10,0.62)	5 (0.11)	0.10 (−0.34,0.54)	5 (0.56)	0.25 (−0.25,0.75)	6 (0.26)
Purdue Pegboard (points)	13.67 (5.89)	−1.20 (−5.71,3.31)	5 (0.50)	0.40 (−0.71,1.51)	5 (0.37)	−0.33 (−3.95,3.28)	6 (0.82)
SIP (%)	8.12 (4.26)	−0.79 (−6.81,5.24)	6 (0.75)	3.65 (−1.01,8.31)	6 (0.10)	2.86 (−2.38,8.10)	6 (0.22)
Laboratory Tests							

	Baseline	Treatment (Mean change from baseline to 24 weeks)		Washout (Mean change from 24 weeks to 40 weeks)		Entire Study (Mean change from baseline to 40 weeks)	
	Mean (Standard Deviation)	Mean (95% confidence interval)	n (p-value)	Mean (95% confidence interval)	n (p-value)	Mean (95% confidence interval)	n (p-value)
HDL (mg/dL)	54.17 (21.01)	6.20 (−3.23,15.63)	5 (0.14)	−5.40 (−28.24,17.44)	5 (0.55)	−2.17 (−17.12,12.78)	6 (0.72)
Triglycerides (mg/dL)	145.83 (78.85)	−46.60 (−132.4,39.20)	5 (0.21)	19.60 (−32.55,71.75)	5 (0.36)	−9.17 (−76.88,58.54)	6 (0.74)
HbA1C (%)	5.58 (0.53)	−0.08 (−0.47,0.31)	5 (0.60)	0.16 (−0.14,0.46)	5 (0.21)	0.12 (−0.11,0.34)	6 (0.24)
Glucose (mg/dL)	92.67 (13.75)	−7.20 (−18.59,4.19)	5 (0.15)	2.60 (−3.77,8.97)	5 (0.32)	−5.17 (−17.52,7.19)	6 (0.33)
Testosterone (ng/dL)	396.67 (164.97)	247.33 (45.42,449.24)	3 (0.03)	−242.67 (−638.0,152.6)	3 (0.12)	4.67 (−251.3,260.6)	3 (0.94)

Legend.DEXA Lean: Lean body mass measured by dual energy x-ray absorptiometry; MMT: average Manual Muscle Testing score across all muscles tested; QMA: Average Quantitative Muscle Assessment score expressed across all muscles tested as a percentage of the expected normal value for age, gender, and height; FVC: Forced vital capacity; Ascend: Time to ascend 4 steps; Descend: Time to descend 4 steps; SIP: Sickness Impact Profile; HDL: High-Density Lipoprotein; HbA1C: Hemoglobin A1c level. Six minute walk testing was added after this cohort completed the study.

Table 4

Mean changes in measures of muscle mass and strength, functional testing and quality-of-life, laboratory testing, and gastrointestinal survey scores (for N=9 Cohort 2).

	Baseline	Treatment (Mean change from baseline to 24 weeks)		Washout (Mean change from 24 weeks to 40 weeks)		Entire Study (Mean change from baseline to 40 weeks)	
	Mean (Standard Deviation)	Mean (95% confidence interval)	n (p-value)	Mean (95% confidence interval)	n (p-value)	Mean (95% confidence interval)	n (p-value)
Muscle Mass and Strength							
DEXA Lean (kg)	43.55 (11.67)	2.27 (0.96,3.59)	9 (<0.01)	−1.03 (−1.84, −0.23)	9 (0.02)	1.24 (−0.07,2.55)	9 (0.06)
MMT	4.11 (0.40)	0.10 (−0.21,0.41)	9 (0.49)	0.02 (−0.19,0.23)	9 (0.84)	0.12 (−0.04,0.27)	9 (0.12)
QMA	56.22 (19.34)	−0.74 (−6.25,4.77)	9 (0.77)	0.48 (−3.87,4.83)	9 (0.80)	−0.26 (−5.33,4.82)	9 (0.91)
BMI (kg/m^2)	22.65 (4.05)	0.65 (−0.04,1.33)	9 (0.06)	−0.30 (−0.82,0.21)	9 (0.21)	0.34 (−0.48,1.17)	9 (0.37)
Functional Testing and QOL							
Hand Grip (kgf)	11.09 (6.97)	−0.87 (−3.10,1.36)	9 (0.40)	−0.33 (−1.70,1.04)	9 (0.59)	−1.20 (−2.62,0.22)	9 (0.09)
FVC (L)	3.52 (0.79)	−0.03 (−0.23,0.18)	9 (0.77)	0.07 (−0.03,0.16)	9 (0.13)	0.04 (−0.17,0.26)	9 (0.66)
Walk 30 feet (sec)	5.01 (3.81)	0.39 (−0.15,0.93)	9 (0.14)	−0.44 (−1.22,0.33)	9 (0.22)	−0.06 (−0.51,0.40)	9 (0.79)
Six Minute Walk (feet)	1414.86 (444.76)	116.29 (−56.9,289.5)	7 (0.15)	−2.00 (−73.4,69.4)	7 (0.95)	114 .29 (−43.8,272.4)	7 (0.13)
Ascend (sec)	2.69 (2.96)	0.33 (−0.01,0.68)	9 (0.06)	−0.13 (−0.47,0.21)	9 (0.39)	0.20 (−0.04,0.44)	9 (0.09)
Descend (sec)	3.07 (3.87)	−0.09 (−0.46,0.29)	9 (0.60)	−0.34 (−1.04,0.36)	9 (0.29)	−0.43 (−1.35,0.48)	9 (0.31)
Purdue Pegboard (points)	12.22 (3.15)	0.33 (−1.10,1.77)	9 (0.61)	0.63 (0.00,1.25)	8 (0.05)	1.00 (−0.55,2.55)	8 (0.17)

	Baseline	Treatment (Mean change from baseline to 24 weeks)		Washout (Mean change from 24 weeks to 40 weeks)		Entire Study (Mean change from baseline to 40 weeks)	
	Mean (Standard Deviation)	**Mean (95% confidence interval)**	**n (p-value)**	**Mean (95% confidence interval)**	**n (p-value)**	**Mean (95% confidence interval)**	**n (p-value)**
SIP (%)	10.23 (4.68)	−1.48 (−3.68,0.71)	9 (0.16)	−0.59 (−2.91,1.73)	9 (0.57)	−2.08 (−4.80,0.64)	9 (0.12)
Laboratory Tests							
HDL (mg/dL)	47.11 (11.38)	4.33 (−1.62,10.29)	9 (0.13)	−0.44 (−7.22,6.33)	9 (0.88)	3.89 (−1.82,9.60)	9 (0.15)
Triglycerides (mg/dL)	136.56 (50.12)	−47.78 (−69.9,−25.65)	9 (<0.01)	45.67 (14.95,76.38)	9 (<0.01)	−2.11 (−28.59,24.36)	9 (0.86)
HbA1C (%)	5.37 (0.20)	−0.19 (−0.33, −0.05)	9 (0.01)	0.21 (0.09,0.33)	9 (<0.01)	0.02 (−0.08,0.13)	9 (0.65)
Glucose (mg/dL)	85.83 (6.32)	−3.83 (−10.46,2.80)	9 (0.22)	2.33 (−4.78,9.45)	9 (0.47)	−1.50 (−5.73,2.73)	9 (0.44)
Testosterone (ng/dL)	475.00 (96.87)	169.25 (4.68,333.82)	4 (0.05)	*	*	*	*

Legend. DEXA Lean: Lean body mass measured by dual energy x-ray absorptiometry; MMT: average Manual Muscle Testing score across all muscles tested; QMA: Average Quantitative Muscle Assessment score expressed across all muscles tested as a percentage of the expected normal value for age, gender, and height; FVC: Forced vital capacity; Ascend: Time to ascend 4 steps; Descend: Time to descend 4 steps; SIP: Sickness Impact Profile; HDL: High-Density Lipoprotein; HbA1C: Hemoglobin A1c level.

*40 week testosterone data are not available for this cohort.