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STUDY PROTOCOL

Study of Testosterone and rHGH in FSHD (STARFiSH): A Proof-of-Concept Study

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Protocol Synopsis	
Protocol Title	Study of Testosterone and rHGH in FSHD: A Proof-of-Concept Study
Acronym	STARFiSH
Clinical Phase	Phase 1
Study Population	Subjects will be ambulatory men (ages 18 to 65) with FSHD
Funding	Planned NIH
Study Drug	Recombinant human growth hormone (Genotropin®) Testosterone enanthate injection (generic)
Study Drug Supplier	Pfizer (Genotropin®)
Number of Subjects	20 subjects
Number of Study Centers	1 – University of Rochester Medical Center FSHD clinic
Duration of Study	36 weeks total (24 weeks on study drug)
Primary Objective	To examine the safety and tolerability of rHGH and testosterone in adult male patients with FSHD.
Secondary Objectives	▪ To examine the pharmacokinetic effects of rHGH and testosterone on serum levels of free and total testosterone, IGF-1, thyroid function, luteinizing hormone and follicle stimulating hormone. ▪ To examine the effect of rHGH and testosterone on total and regional lean body mass.
Exploratory Objectives	To examine the effects of rHGH and testosterone on multiple measures of clinical function including ambulation, strength, pulmonary function, and patient reported disease-burden.
Evaluations	**Exploratory efficacy outcome measures**: Measures of preliminary efficacy include the following (all measured as the change from baseline to week 24): 1. Composite Quantitative Muscle Testing (QMT) score 2. Composite Manual Muscle Testing (MMT) score 3. FSHD Clinical Outcome Measure (FSHD-COM), total and individual test scores 4. FSHD-Health Index (FSHD-HI), disease-specific patient-reported outcome measure 5. Forced Vital Capacity (FVC) 6. Epworth Sleepiness Scale 7. Fatigue Severity Scale 8. Dual Energy X-Ray Absorptiometry (DEXA) Lean Body Mass (total and regional) 9. PROMIS-57 10. FSHD daily exercise questionnaire. 11. Beck Depression Inventory (BDI) 12. Six minute walk distance 13. International Physical Activity Questionnaire **Feasibility outcome measures**: 1. Willingness to travel to Rochester, NY for a screening/baseline visit

	2. Number of consented subjects 3. Number of completed rHGH injections per enrolled participant 4. Number of completed testosterone injections per enrolled participant 5. Ability of participants to administer study drug 6. Number of completed study visits per participant 7. Number of subjects that completed the study without drug discontinuation 8. Number of subjects who completed the study **Safety outcome measures**: 1. Changes from baseline in laboratory test results, vital signs, and EKG results 2. Occurrence of serious adverse events 3. Occurrence of non-serious adverse events
Significance/Relevance	The most significant symptoms to FSHD patients are related to muscle dysfunction and may be amendable to testosterone/rHGH therapy. In 2012 a cross-sectional study of 328 FSHD patients was completed to identify the symptoms most important to this population. Six symptomatic themes were identified as having a prevalence of 90% or higher. These FSHD themes included: 1) problems with shoulders or arms; 2) the inability to do activities; 3) fatigue; 4) back, chest, and abdomen weakness; 5) limitations with mobility or walking; and, 6) changed body image due to disease. In addition to being highly prevalent in FSHD, these themes were also identified as having the highest impact on the daily lives of FSHD patients. Testosterone/rHGH therapy has been previously shown to improve respiratory function, lean body mass, strength, and aerobic endurance in healthy elderly men. If these effects also occur in FSHD patients, many (if not all) of the above life altering symptoms could be improved. The proposed study will evaluate testosterone/rHGH therapy for the first time in an FSHD population. The intervention of testosterone paired with rHGH for FSHD is novel and, despite solid evidence in other human populations, has never been implemented in FSHD. If safety and proof-of-concept is demonstrated, the data from this study will form the basis for initiating a larger efficacy trial of combination therapy in FSHD. The identification of an efficacious and safe therapeutic approach that reduces a decline in clinically relevant function, strength, and quality-of-life in muscular dystrophy would represent a significant advance in the clinical management of this population.
Study Design	This study is a proof-of-concept study to evaluate the potential efficacy of daily testosterone plus rHGH injections in men with FSHD. Subjects (n=20) will be assigned to receive active drug (Genotropin® and testosterone) for 24 weeks while being closely monitored. Analyses will be conducted after the last subject enrolled has completed their last scheduled study visit (at 36 weeks after a 12 week washout period).
Sample Size Considerations	The primary tolerability outcome variable is the ability to take combination study medication for 24 weeks and complete the 24 week treatment period. The criterion for declaring combination

treatment well tolerated will be based on a hypothesis test that compares the observed tolerability rate against a tolerability rate that would be considered unacceptably low. We believe that 70% is a reasonable choice for the unacceptably low tolerability rate in this context. A test based on the binomial distribution will be performed for H0: $\pi \leq 0.70$ vs. H1: $\pi > 0.70$, where π is the true probability of tolerability. The decision rule will be to reject the null hypothesis of unacceptable tolerability if the number of subjects tolerating the dosage is 18 (out of 20) or greater. This rule will provide 80% power to detect that the dosage is tolerable (has a tolerability rate > 70%) if the true tolerability rate is 92%. The actual significance level of this test is 3.6%.

The table below provides information on the precision with which the incidence of a particular adverse event can be estimated as well as the probability of observing at least one such event during the trial given different values for the true incidence of the adverse event in the target FSHD population receiving combination therapy. A sample size of 20 participants will yield a 95% upper confidence bound for the incidence that is within approximately 20% of the observed incidence. It will also make it very likely that an adverse event with a true incidence ≥ 15% will be observed in at least one subject during the trial.

Estimation of adverse event incidence with n = 20 participants.

Observed Adverse Event Incidence	95% Upper Confidence Bound	True Adverse Event Incidence	Probability of Observing at Least 1 Adverse Event
5%	21.6%	5%	26.1%
10%	28.3%	10%	60.8%
15%	34.4%	15%	82.4%
20%	40.1%	20%	93.1%
25%	45.6%	25%	98.0%
30%	50.8%	30%	99.2%

For lean body mass, an estimated standard deviation of 1.6 kg was derived using data on 24-week change from participants in our ongoing longitudinal study of FSHD progression (PI: Heatwole, U01AR065119). Assuming a standard deviation of 1.6 kg meters for the this outcome variable, a sample size of 18 participants will provide 85% power to detect a mean change of 1.2 kg , using a t-test and a 5% significance level (two-tailed). A sample size of 20 participants will allow for an anticipated attrition rate of 10%.

For the 6MWT, an estimated standard deviation of 42.3 meters was derived using data on 24-week change from participants in our ongoing longitudinal study of FSHD progression. Assuming a standard deviation of 40 meters for this outcome variable, a sample size of 18 participants will provide 85% power to detect a mean change of 30 meters, using a t-test and a 5% significance level (two-tailed). Recent studies in chronic obstructive pulmonary disease[1,2], coronary artery disease[3], and Duchenne muscular dystrophy[4]

	support a distance of 25-35 meters as representing a minimal clinically important change. A sample size of 20 participants will allow for an anticipated attrition rate of 10%.
Route & Dosage Form	Testosterone enanthate (in oil) will be delivered via intramuscular injections every 2 weeks. rHGH (Genotropin®) will be given by subcutaneous injections
Dosage	Testosterone enanthate, 140 mg every two weeks. Genotropin®, 5.0 µg/kg/day (calculated using the patient's pre-entry weight)
Inclusion Criteria	▪ Males ages 18 to 65 years ▪ Moderately affected, symptomatic, ambulatory, FSHD (genetically confirmed or clinical symptoms suggestive of FSHD with a first degree relative with genetically confirmed FSHD) ▪ Hematocrit of ≤ 50% ▪ Prostate-specific antigen ≤ 4.0 ng/ml (or ≤ 3.0 ng/ml if the participant is at elevated risk of prostate cancer (e.g. the participant has a first-degree relative with prostate cancer) ▪ Fasting blood glucose <126 mg/dl ▪ Participants will be able to walk continuously for six minutes (cane, orthoses allowed) and be able to independently administer an IM and SC injection (or have a family member who is capable and willing to administer these injections
Exclusion Criteria	▪ Diabetes, obesity (BMI>35 kg/m2), or cardiovascular disease (heart failure, coronary artery disease, uncontrolled hypertension, untreated hypercholesterolemia) ▪ Untreated thyroid disease ▪ Deep vein thrombosis ▪ Untreated severe sleep apnea ▪ Past pituitary disease ▪ Significant musculoskeletal injury and/or pain that affects walking ▪ A systolic blood pressure over 160 or a diastolic pressure over 100 ▪ Plans to dramatically change exercise habits ▪ Liver disease ▪ Psychiatric disease ▪ Renal disease ▪ Severe lower urinary tract symptoms (International Prostate Symptom Score (IPSS)> 19) ▪ Cancer (other than basal cell skin cancer) ▪ An active desire to conceive, heavy alcohol use (greater than 50 g/day) ▪ Current testosterone or HGH use ▪ Testosterone level of ≥ 1100 ng/dl ▪ Current use of medications that interfere with the growth hormone or gonadal endocrine axis.

1.0 STUDY OBJECTIVES AND MEASURES

1.1 Primary Objective

To examine the safety and tolerability of rHGH and testosterone in adult male patients with FSHD.

1.2 Secondary Objectives

1) To examine the pharmacokinetic effects of rHGH and testosterone on serum levels of free and total testosterone, IGF-1, thyroid function, luteinizing hormone and follicle stimulating hormone.
2) To examine the effect of rHGH and testosterone on total and regional lean body mass.

1.3 Exploratory Objectives

To examine the effects of rHGH and testosterone on multiple measures of clinical function including ambulation, strength, pulmonary function, and patient reported disease-burden.

1.4 Outcome measures

Feasibility outcome measures:

1. Willingness to travel to Rochester, NY for a screening/baseline visit
2. Number of consented subjects
3. Number of completed rHGH injections per enrolled participant
4. Number of completed testosterone injections per enrolled participant
5. Ability of participants to administer study drug
6. Number of completed study visits per participant
7. Number of subjects that completed the study without drug discontinuation
8. Number of subjects who completed the study

Safety outcome measures:

1. Changes from baseline in laboratory test results, vital signs, and EKG results
2. Occurrence of serious adverse events
3. Occurrence of non-serious adverse events

Exploratory efficacy outcome measures:

Composite Quantitative Muscle Testing (QMT) score
Composite Manual Muscle Testing (MMT) score
FSHD Clinical Outcome Measure (FSHD-COM), total and individual test scores
FSHD-Health Index (FSHD-HI), disease-specific patient-reported outcome measure
Forced Vital Capacity (FVC)
Epworth Sleepiness Scale
Fatigue Severity Scale
Dual Energy X-Ray Absorptiometry (DEXA) Lean Body Mass (total and regional)
PROMIS-57
FSHD daily exercise questionnaire.
Beck Depression Inventory (BDI)
Six minute walk distance
International Physical Activity Questionnaire

2.0 BACKGROUND & RATIONALE

2.1 Facioscapulohumeral muscular dystrophy

Facioscapulohumeral muscular dystrophy (FSHD) is the second most common form of adult muscular dystrophy with a prevalence of 1:15,000-1:20,000.[5,6] The clinical manifestations of FSHD include steady progressive weakness of the face, shoulders, arms, and hip girdle muscles and life altering fatigue, impaired ambulation, respiratory decline, social limitations, and activity impairment related to muscle weakness. In a recent paper of functional impairment in FSHD, patients were reported to have a loss of strength between 1 and 4% per year and a 24% chance of developing a need for a wheelchair over a six year interval.[7] Currently, there is no known disease modifying therapy for FSHD that can improve or limit functional decline in ambulation.

2.2 Anabolic Effects in FSHD

We hypothesize that the anabolic benefits of testosterone and human growth hormone observed in healthy adults will also occur in FSHD participants. Indeed, our studies of albuterol in FSHD demonstrate that FSHD muscle is responsive even to mildly anabolic agents.[8,9] We hypothesize that the side effect profile of combination therapy in FSHD will be acceptable and comparable to that previously demonstrated in healthy adults. If treatment is ultimately found to limit the rate of functional decline in FSHD, it would represent a significant therapeutic advance for patients who currently struggle with this muscular dystrophy.

2.3 Proposed Intervention

2.3.1 Human Growth Hormone

Human Growth Hormone (HGH) is a naturally occurring peptide hormone that is produced in the pituitary gland of men and women. Like testosterone, HGH can stimulate cell growth and regeneration.[10] In HGH deficient states, patients experience exercise intolerance, low bone mineral density, changes in body composition, and a worsening cholesterol profile.[11] HGH supplementation can ameliorate these impairments. Recombinant HGH (rHGH) is a synthesized preparation of HGH that has been used to treat children and adults with growth hormone deficiency, as well as those with muscle wasting, Turner syndrome, Prader-Willi syndrome, chronic renal failure, and idiopathic short stature.[10,12-15]

2.3.2 Testosterone

Testosterone is a naturally occurring androgen that is produced in both men and women. Testosterone promotes protein synthesis and has anabolic effects on both muscle and bone.[16] It is commonly utilized for men with hypogonadism and conditions associated with low or no endogenous testosterone.[17] It is also recommended for men to improve libido and erectile dysfunction.[18] In women, testosterone supplementation has been used for muscle atrophy associated with acquired immune deficiency syndrome, inoperable metastatic breast cancer, low libido, sexual dysfunction, muscle wasting, and as a postmenopausal therapy.[19-25] The Endocrine Society currently recommends testosterone to: 1) increase muscle strength and lean body mass in patients with HIV; and 2) improve bone mineral densities in patients receiving high dosages of glucocorticoids.[18] In a prior study, testosterone in isolation has been shown to be safe and increase lean body mass, reduce body fat, and improve basal metabolic rate in a heterogeneous group of adult muscular dystrophy population (including a FSHD participant) with normal baseline testosterone levels. In this study, results were seen after 3 months of treatment and were comparable to the results demonstrated in a group of normal men receiving the same therapy.[26] In a second study of 40 patients with myotonic dystrophy, testosterone in isolation was found to be safe, tolerable, and able to improve both creatinine excretion and lean body mass while not statistically improving overall strength.[27]

2.3.3 Combination Therapy and Implications for FSHD

Over the last 12 years, researchers have studied the utility of testosterone combined with recombinant human growth hormone to increase strength and lean muscle mass. Large scale clinical trials, mostly in men, have found testosterone and rHGH in combination to be well tolerated and effective in improving respiratory function, lean body mass, strength, and aerobic endurance.[20,28-31] Between 2002 and 2009, three large placebo-controlled human trials evaluating 323 participants were conducted with results demonstrating the safety and benefit of combination therapy over monotherapy or placebo (Table 1).[20,28,29] Results from these studies suggest a synergistic effect of these two agents for improving muscle function in humans.[20,28,29]

In the HORMA (Hormonal Regulators of Muscle and Metabolism in Aging) study, researchers compared six different dosage combinations of testosterone and rHGH to identify the most effective dose combination.[29-31] Testosterone gel at 5g/day and 10g/day was paired with rHGH at 0 μg/kg/day (placebo), 3μg/kg/day, and 5μg/kg/day. The most pronounced benefits in body composition, strength, endurance, and reduction in fasting triglycerides were seen with the combined higher dosages of both medications.[29-31]

The positive effects of combined testosterone/rHGH therapy have also been observed in younger healthy populations. In a randomized, double-blind, placebo-controlled, 8-week trial of recreational trained athletes, participants were assigned testosterone, growth hormone, placebo, or combined therapy. A greater improvement in sprint capacity was seen with combination therapy than with any other therapy.[32] Still other studies have observed markedly increased protein synthesis in men receiving combination therapy. [18,20,32,33] This therapeutic approach is one of the few documented methods shown via clinical trial to reduce declines in both lean muscle mass and physical strength.

Despite promising effects on muscle strength, function, and metabolism, a study of testosterone/rHGH in a population of muscular dystrophy patients has never been performed. We hypothesize that reductions in strength, endurance, and lean body mass will be lessened overtime in response to combination therapy in FSHD. If gains in muscular and physical function are of similar magnitude in FSHD as they have been in other populations, this discovery would significantly improve therapeutic options for FSHD patients and may provide an option to limit progressive muscle weakness and functional decline in other musculoskeletal populations.[34]

Three Clinical Studies of Testosterone/ Growth Hormone Combination Therapy					
Title	**Treatment**	**N**	**Body Composition (DEXA)**	**Strength**	**Aerobic Capacity**
Growth Hormone and Sex Steroid Administration in Healthy Aged Women and Men: A Randomized Clinical Trial (JAMA)	rHGH +placebo; sex steroid*+ placebo; rHGH + sex steroid*	131	**4.3 kg increase** in lean body mass in men treated with T/rHGH; T/rHGH produced the greatest reductions in body fat	**6.8% increase** in strength in men treated with T/rHGH	**8.6% improvement** in graded treadmill exercise testing (Vo2Max) in T/rHGH Group
The Effects of Growth Hormone and/or Testosterone in Healthy Elderly Men: A Randomized Controlled Trial (JCEM)	rHGH +placebo; T + placebo; rHGH + T; Placebo	80	**1.8 kg increase** in lean body mass in men treated with T/rHGH; This group also had the greatest reduction in body fat	**4.06 Nm** increase in knee flexion torque in men treated with T/rHGH	**23% improvement** of VO2Max in T/rHGH vs. placebo
Testosterone and Growth Hormone Improve Body Composition and Muscle Performance in Older Men (JCEM)	Low or High dose T groups paired with placebo or 1 of 2 dosages of rHGH (3,5 µg/kg/day)	112	**2.6 kg increase** in lean body mass with the high dose T/rHGH; This group also had the greatest reduction in body fat	**29% increase** in composite strength in men treated with high dose T/rHGH	**140 second improvement** in cycle endurance in high dose T/rHGH group
* sex steroid= testosterone for men, estradiol/medroxyprogesterone for women; T= testosterone; rHGH= recombinant Human Growth Hormone					

3.0 INVESTIGATIONAL PLAN

3.1 Study Design

STARFiSH is a proof-of-concept, single-center, open-label study of daily human growth hormone (Genotropin®, 5.0 µg/kg via subcutaneous injection) and testosterone (testosterone enanthate, 140mg via intramuscular injection every two weeks) for 24 weeks in men with FSHD with a 12 week washout period. This protocol is based on three prior controlled clinical trials of combination therapy in humans and includes modifications to best accommodate the FSHD population.[20,28,29] A total of 20 subjects will be enrolled at the University of Rochester Medical Center in Rochester, NY.

3.2 Rationale for Combination Therapy & Proposed Dosages

We will use the equivalent dosage of testosterone and rHGH that was found to be safe and most effective for men in the multicenter, dose-finding HORMA study.[29-31]
Additional clinical studies of combination therapy using higher average dosages of testosterone paired with rHGH provide support for our rHGH dosage selection.[20,28] In these studies, while clinical benefit was observed with higher rHGH dosages, adverse events attributed to higher rHGH dosages limited patient tolerability. In one trial, a mean dosage of 6.52 µg/kg/day of rHGH with testosterone was administered to patients with an average mass of 79.7 kg.[28] While clear improvements in strength, body composition, and aerobic capacity were seen with this combination therapy, 41% of patients had mild adverse events attributed to the higher dosage of rHGH. [28] With rHGH dosage reductions, these mild adverse events resolved. Similarly, in another study, patients on combination therapy experienced improvements with graded treadmill exercise testing; however, at the higher mean rHGH dosage of 8.57 µg/kg/day, 32% of men experienced carpal tunnel symptoms.[20] Conversely, HORMA investigators found that the incidence of carpal tunnel symptoms occurred in only 1 of 37 participants (3%) using testosterone paired with an rHGH dosage of 5.0 µg/kg/day (the dosage selected for our study).[29]

A prior dose finding study using HGH in elderly people with hypothalamic-pituitary disease also supports a 5.0 µg/kg/day dosing strategy.[11] Researchers tried patients on different dosages of HGH including 0.17 mg/day, 0.33 mg/day, and 0.5 mg/day. Patients experienced increases in lean body mass and IGF-1 levels using all dosages, but did not have added benefit between the 0.33 mg/day and the 0.5 mg/day dosing. Furthermore, while no patients experienced a major adverse event, three patients on the higher 0.5 mg/day dosage had adverse events attributed to HGH. Using an average baseline mass of 83 kg for the study patients, the optimal tolerated dosage of HGH in this population was estimated to be between 3.98 µg/kg/day and 6.02 µg/kg/day. For adults with growth hormone deficiency, the recommended starting dosage of Genotropin® is 0.040 mg/kg/week (5.7 µg/kg/day); a dosage that is well tolerated, widely used, and above our selected dosage of 5.0 µg/kg/day.

The use of 140 mg of testosterone enanthate IM given every two weeks is supported by prior research and clinical data. In the HORMA study, researchers utilized rHGH combined with 10 grams of 1% testosterone transdermal gel.[29] This combination created the most pronounced therapeutic response in adult males while being found to be both safe and well tolerated. At a 10% systemic absorption this equates to a total dosage of 140 mg of testosterone enanthate over 14 days (the exact dosage that we have chosen for our study). This dosage of testosterone is also similar to what is commonly utilized in clinical practice. The Endocrine Society recommends that men with reduced testosterone levels be treated with testosterone supplementation. Specifically, the Endocrine Society recommends a starting dosage of 150-200 mg of testosterone enanthate given every 2 weeks via intramuscular injection.[18] While our selected dosage is slightly lower (140 mg every two weeks) it will be administered via the identical mechanisms and frequencies commonly used in clinical practice.

3.3 Rationale for Method of Administration

Participants will receive testosterone enanthate (in oil) via intramuscular injection every two weeks. This preparation and its intramuscular delivery mechanism has been extensively studied, utilized broadly for patients with hypogonadism, and is the exact preparation/delivery mechanism that was paired with rHGH and utilized in a study of 131 healthy men and women published in JAMA.1 In general, intramuscular preparations of testosterone have several advantages over topical (i.e., buccal, cream, patch, mucoadhesive) testosterone preparations. Namely, intramuscular preparations are substantially more affordable and have a more predictable therapeutic absorption rate compared to topical preparations. rHGH (Genotropin®) will be given by subcutaneous injections using the Genotropin Pen® delivery device. This device has a dial to select the proper dose of study drug and a dose display directly on the Pen. Participants will be given a document detailing the use of the Genotropin Pen® and will be taught how to use the Pen during their inpatient visits.

3.4 Rationale for Effect and Sample Size

The primary tolerability outcome variable is the ability to take combination study medication for 24 weeks and complete the 24 week treatment period. The criterion for declaring combination treatment well tolerated will be based on a hypothesis test that compares the observed tolerability rate against a tolerability rate that would be considered unacceptably low. We believe that 70% is a reasonable choice for the unacceptably low tolerability rate in this context. A test based on the binomial distribution will be performed for H0: $\pi \leq 0.70$ vs. H1: $\pi > 0.70$, where π is the true probability of tolerability. The decision rule will be to reject the null hypothesis of unacceptable tolerability if the number of subjects tolerating the dosage is 18 (out of 20) or greater. This rule will provide 80% power to detect that the dosage is tolerable (has a tolerability rate > 70%) if the true tolerability rate is 92%. The actual significance level of this test is 3.6%.
The table below provides information on the precision with which the incidence of a particular adverse event can be estimated as well as the probability of observing at least one such event during the trial given different values for the true incidence of the adverse event in the target FSHD population receiving combination therapy. A sample size of 20 participants will yield a 95% upper confidence bound for the incidence that is within approximately 20% of the observed incidence. It will also make it very likely that an adverse event with a true incidence ≥ 15% will be observed in at least one subject during the trial.

Estimation of adverse event incidence with n = 20 participants.

Observed Adverse Event Incidence	95% Upper Confidence Bound	True Adverse Event Incidence	Probability of Observing at Least 1 Adverse Event
5%	21.6%	5%	26.1%
10%	28.3%	10%	60.8%
15%	34.4%	15%	82.4%
20%	40.1%	20%	93.1%
25%	45.6%	25%	98.0%
30%	50.8%	30%	99.2%

For lean body mass, an estimated standard deviation of 1.6 kg was derived using data on 24-week change from participants in our ongoing longitudinal study of FSHD progression (PI: Heatwole, U01AR065119). Assuming a standard deviation of 1.6 kg meters for the this outcome variable, a sample size of 18 participants will provide 85% power to detect a mean change of 1.2 kg , using a t-test and a 5% significance level (two-tailed). A sample size of 20 participants will allow for an anticipated attrition rate of 10%.

For the 6MWT, an estimated standard deviation of 42.3 meters was derived using data on 24-week change from participants in our ongoing longitudinal study of FSHD progression. Assuming a standard deviation of 40 meters for this outcome variable, a sample size of 18 participants will provide 85% power to detect a mean change of 30 meters, using a t-test and a 5% significance level (two-tailed). Recent studies in chronic obstructive pulmonary disease[1,2], coronary artery disease[3], and Duchenne muscular dystrophy[4] support a

distance of 25-35 meters as representing a minimal clinically important change. A sample size of 20 participants will allow for an anticipated attrition rate of 10%.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Subject Population

Experienced investigators will be responsible for recruitment and follow-up of 20 subjects for this clinical trial. Participants will be moderately affected, ambulatory, FSHD men ages 18 to 65. All patients will be symptomatic and have genetically confirmed FSHD or clinical symptoms suggestive of FSHD with a first degree relative with genetically confirmed FSHD. Complete inclusion and exclusion eligibility criteria are listed in Sections 4.2 & 4.3. To be eligible for enrollment into this study, subjects must meet all of the following eligibility criteria.

4.2 Inclusion Criteria

- Males ages 18 to 65 years
- Moderately affected, symptomatic, ambulatory, FSHD (genetically confirmed or clinical symptoms suggestive of FSHD with a first degree relative with genetically confirmed FSHD)
- Hematocrit of ≤ 50%
- Prostate-specific antigen ≤ 4.0 ng/ml (or ≤ 3.0 ng/ml if the participant is at elevated risk of prostate cancer (e.g. the participant has a first-degree relative with prostate cancer)
- Fasting blood glucose <126 mg/dl
- Participants will be able to walk continuously for six minutes (cane, orthoses allowed) and be able to independently administer an IM and SC injection (or have a designated person such as a family member, caregiver, or friend who is capable and willing to administer these injections

4.3 Exclusion Criteria

- Diabetes, Obesity (BMI>35 kg/m2), or cardiovascular disease (Heart failure, coronary artery disease, uncontrolled hypertension, untreated hypercholesterolemia)
- Untreated thyroid disease
- Deep vein thrombosis
- Untreated severe sleep apnea
- Past pituitary disease
- Significant musculoskeletal injury and/or pain that affects walking
- A systolic blood pressure over 160 or a diastolic pressure over 100
- Plans to dramatically change exercise habits
- Liver disease
- Psychiatric disease
- Renal disease
- Severe lower urinary tract symptoms (International Prostate Symptom Score (IPSS)> 19)
- Cancer (other than basal cell skin cancer)
- Plans to conceive, heavy alcohol use (greater than 50 g/day)
- Current testosterone or HGH use
- Testosterone level of ≥ 1100 ng/dl
- Current use of medications that interfere with the growth hormone or gonadal endocrine axis.

4.4 Recruitment Process

Volunteers from diverse ethnic and racial backgrounds will be recruited using local and nationwide recruitment tools. These individuals will be evaluated at the University of Rochester. Recruitment media will include: recruitment websites and newsletters (e.g., Strong Health's Clinical Trials website, websites and newsletters for the Fields Center for FSHD & Neuromuscular Research, the Muscular Dystrophy Association, and the FSH Society), clinicaltrials.gov, and direct mailings through the *National Registry of Myotonic Dystrophy and*

Facioscapulohumeral Dystrophy Patients and Family Members (RSRB #12163).[35] This National registry is headquartered at the University of Rochester and has ~748 members with FSHD 228 meet age and gender eligibility criteria. Participants will also be recruited through The University of Rochester FSHD clinic 39/75 active patients meet age and gender eligibility criteria] and through their participation in current and prior research initiatives at the University of Rochester. One such study is a NIH-funded disease progression evaluation of 40 FSHD patients at the University of Rochester (PI: Heatwole: U01AR065119). To date, we have successfully recruited and obtained consent for the full number of FSHD patients for this study and 21 of these participants currently meet gender and age eligibility criteria. The University of Rochester has a history of successfully recruiting patients for FSHD clinical trials. In one such instance, University of Rochester researchers working with The Ohio State University enrolled 90 FSHD patients for a clinical trial of albuterol.[8] The male patients from that study met comparable (albeit not identical) eligibility criteria to those proposed in our study. If needed, we will also request referrals from our neuromuscular collaborators including researchers from Boston, Baltimore, Columbus, Salt Lake City, Seattle, Kansas City, Gainesville, and Stanford.

4.5 Subject Identification Numbers
The participants will assigned a unique, coded identification number at the Screening visit. This Subject ID will be included on all data forms for all visits.

4.6 Subject Withdrawal
Subjects have the right to discontinue study drug and/or study participation at any time and for any reason. The investigator also has the right to discontinue study drug or subject's participation if he/she feels it is in the subject's best interest (e.g. clinical condition worsening, adverse events, subject is not following protocol requirements, etc). A subject will be considered to have withdrawn from the study in the following circumstances: death, lost-to-follow-up, withdrawal of informed consent or if site investigator feels study participation should be discontinued. If discontinuation of study drug is related either to an adverse event or serious adverse event, details must be documented per Adverse Event Reporting guidelines in Section 9.0.

4.7 Costs to the Subject
Subjects and their insurance will not incur any costs as a result of participating in this study. A grant through the National Institutes of Health (NIH) will pay for the procedures associated with the study as well as testosterone. Genotropin will be provided by Pfizer.

4.8 Payment for Participation
Study participants will be reimbursed for travel and lodging expenses (up to $500.00 per visit). Patients will receive a payment of $100 per visit for four of the five study visits (for a total of $400). Patients must complete a visit to receive payment for that visit. Patients will not receive a payment for the screening/baseline visit. If a family member will be assisting with study drug administration, their travel expenses will also be reimbursed up to $500 (for the initial visit only).

*The study will use a subject payment system called Advarra Participant Payments. The system allows three ways to provide payment: a reloadable debit card; direct deposit; or mailed paper checks. The study team will help patients create a subject profile which will include their name and date of birth. Depending on which payment method a patient chooses, email address and banking information may be required. If patients already have an Advarra account (because they're in another study that uses this system), their existing profile will be used to provide payment. An '**Information Sheet for Advarra Participant Payments"** will be provided to patients for their reference.*

4.9 Return of Individual Research Results
Laboratory results including results from blood tests, urinalysis, ECGs, and DEXA scans will be provided to subjects at their study visit. Patients will be informed if their results suggest that they are in need of further testing. The study doctor/staff will talk with patients about their findings and options. Patients may be asked to follow up with their regular doctor or other specialists for future care.

5.0 STUDY DRUG ADMINISTRATION / ASSIGNMENT

5.1 Formulation
Genotropin® will be supplied by Pfizer Inc. The generic form of testosterone enanthate will be purchased by the investigational pharmacy from a local vendor. Both drugs will be received and dispensed by the Investigational Drug Services unit at the University of Rochester.

5.2 Packaging, Labeling, and Distribution
The University of Rochester, Investigational Drug Services unit will provide packaging, labeling, and distribution to the investigational unit to ensure that each subject has an adequate and appropriate supply of study drug.

5.3 Storage of Study Drug
The investigator will ensure that all study drug supplies are kept in a locked, safe area under appropriate storage conditions with access limited to those directly involved in the study. Drug supplies should not be repackaged in any way. Genotropin® should be stored at controlled refrigerated temperature, 2-8° C (36-46° F). Testosterone should be stored at room temperature.

5.4 Dispensing & Administration

Participants will be given study medication during their baseline visit to take home with them. Compliance will be tracked using a compliance questionnaire and used vials will be collected at each study visit. Medications will be provided by the Investigational Drug Service (IDS) at the University of Rochester. Sharp boxes, syringes, needles, vials, alcohol swabs, and Genotropin Pens and cartridges will be provided to each participant. Administration of therapy will be taught to participants by trained personnel and will fully comply with each medication's labeling instructions. A designated person such as a family member, caregiver, or friend, will also be instructed on study drug administration, if needed. Participants will be given documents, will watch video tutorials, and will be instructed on drug administration at the baseline visit.

Testosterone enanthate: Subjects will receive vials of testosterone enanthate to be administered as one intramuscular injection into the gluteal or thigh muscle. When properly given, intramuscular injections of testosterone enanthate are well tolerated. Care should be taken to slowly inject the preparation deeply into the gluteal or thigh muscle, being sure to follow the usual precautions for intramuscular administration, such as the avoidance of intravascular injection.

Genotropin®: Subjects will be given Genotropin Pen® delivery devices with 5 or 12 mg cartridges. This device has a dial to select the proper dose of study drug and a dose display directly on the Pen. Participants will be instructed on how to use the dial to administer the correct medication dose. Participants will receive Genotropin® using these Pens via subcutaneous injection, as calculated based on body weight at the Screening/Baseline Visit. Subjects will pinch a fold of skin at the injection site, insert the pen at a 90 degree angle, push the black/white injection knob until it clicks, wait 5 seconds, then withdraw Pen. Participants will be given a document detailing the use of the Genotropin Pen® and will be taught how to use the Pen during their inpatient visit.

5.5 Dosing Regimen
Subjects will receive 5ug/kg/day of Genotropin® and 140mg every two weeks of testosterone enanthate for 24 weeks. Subjects will be instructed to administer the Genotropin® after an evening meal.

5.6 Dosage Adjustments
Dosage reductions are permitted at any time during the study.

5.6.1 Dosage Reduction

The investigator should be consulted prior to the subject reducing the dosage of study drug. The safety monitor will review all safety data and based on adverse effects, laboratory profiles, vital signs, or EKG results will recommend that a subject's dosage of study medication be reduced or make recommendations regarding potential withdrawal from the study. Elevations of IGF-1 higher than 400 ng/mL, a total testosterone higher than 1100 ng/dL, or a HCT ≥54% will warrant a reduction in study medication. The Safety Monitor will provide the Investigator with guidance on recommendations to reduce a dosage. A dosage reduction is accomplished by lowering the total daily dosage by 25%, 50%, 75%, or 100% based on the type of adverse event noted and if it was attributed to rHGH and/or testosterone (or more as deemed necessary by the investigator) until symptoms resolve or reduced dosage is tolerated by the subject. Dosage reductions are to be documented on the Dose Management Log.

5.6.2 Dosage Suspension

Administration of the study drug may be interrupted for intolerable adverse effects thought to be related to study drug, intercurrent illnesses or surgery at any time during the study. These situations will be handled on a case-by-case basis. A suspension may last up to two weeks. If a longer suspension is required, the Safety Monitor will be contacted and the situation will be reviewed and approved if appropriate. Subjects will be considered to have permanently discontinued study drug for suspensions lasting longer than 2 weeks without prior approval by the safety monitor. Multiple suspensions throughout the study are allowable in consultation with the safety monitor. Dosage suspensions are to be documented on the Dose Management Log.

5.6.3 Discontinued Study Drug

Subjects who permanently discontinue study drug may be followed in the study per intention to treat. There is no downward titration necessary when the study drug is permanently discontinued. Study drug discontinuations are to be documented on the Dose Management Log.

5.6.4 Missed Doses

Participants will record missed dosage on their medication log. Missed doses will not be replaced and participants will be instructed to continue their dosing regimen as instructed. Missed doses and methods for mitigating future missed doses will be discussed on weekly participant calls.

5.7 Accountability and Compliance of Study Drug

The site investigator or coordinator must maintain accurate records (including dates) of receipt of all study drug from IDS. Drug accountability records must be completed to account for the dispensing of the study drug. Compliance will be assessed by tracking dispensed and unused packets at each in-person visit and by subject self-report at weekly telephone contacts. Subjects will be instructed to return unused study drug to be collected at each in-person visit. The subject will be counseled and, as necessary, re-instructed on proper administration of study drug. Additionally, laboratory studies (e.g. IGF-1 levels and testosterone levels) will be expected to rise with medication use. The absence of a laboratory response will suggest noncompliance with study medication.

5.8 Prior and Concomitant Interventions

Prior and concomitant drugs taken by subjects up to 90 days before the Baseline visit and throughout the duration of the study will be documented and followed for any changes at all visits including in-person and telephone contacts. Documentation of the use and daily dosing of other dietary supplements, including those hypothesized to affect the endocrine access will be employed.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Activities

An overview of the schedule of activities and evaluation is provided in **Table 2.** Following informed consent, participants will have a screening visit. Participants who meet all eligibility requirements will be enrolled and will receive serial in-person assessments at baseline, 8 weeks, 16 weeks, 24 weeks, and 36 weeks. 16 weeks has been shown to be an adequate time to demonstrate both increases in strength and function.[29-31] [32]

Throughout the study, participants will receive weekly phone calls from a clinical coordinator to address any study-related difficulties. All subjects will be followed for the full 36 weeks, if they are willing, regardless of protocol violations or withdrawal of study drug.

Schedule of Study Activities and Testing

	Screening	Baseline	8w	16w	24w	36w
Activity						
On Combination Therapy						
Washout Period						
Informed consent	X					
Documentation of Inclusion/Exclusion criteria	X					
Clinic Visits	X	X	X	X	X	X
Laboratory Testing *	X		X	X	X	X
Study Medication Dispensed		X	X	X		
Dual Energy X-Ray Absorptiometry (DEXA)		X		X	X	X
Six Minute Walk Test	X					
FSHD-COM		X	X	X	X	X
Strength and Functional Testing		X	X	X	X	X
Exercise Log Review			X	X	X	X
Patient-Reported Outcome Measures		X	X	X	X	X
Safety Monitoring						
Vitals **	X	X	X	X	X	X
Physical Exam	X		X	X	X	X
Fundoscopic Exam		X	X	X	X	X
Digital Rectal Exam	X		X	X	X	X
International Prostate Symptom Score	X		X	X	X	X
Quantitative Insulin Sensitivity Check Index		X	X	X	X	X
Side effect questionnaire		X	X	X	X	X
EKG	X		X	X	X	X
Weekly Phone Calls						

* Free and total T levels, IGF-1 (Free/ total), PSA, fasting glucose, chem 14, CK, lipid profile luteinizing hormone, Insulin levels, HGA1c, FSH, CBC, CRP, TSH, and Free T4 levels, urinalysis

** Height, weight, blood pressure, body mass index, pulse, respiratory rate, temperature

6.2 Screening and Baseline Visit

The Screening Evaluations can take place at the same visit or within two weeks of the Baseline visit. The Baseline visit will require an overnight stay at the Clinical Research Center at the University of Rochester. Screening and baseline evaluations will take place after the subject has signed the informed consent document. Study drug will be administered only after the inclusion/exclusion criteria have been fulfilled (e.g. fasting serum glucose, liver function tests, testosterone, hematocrit, serum prostate specific antigen, and 6 minute walk test).

6.2.1 Screening Evaluations

During this visit, the subject will be thoroughly informed about all aspects of the study, including all scheduled visits and activities, and will be requested to sign and date the informed consent prior to performing any study-related procedures.

Subjects will be assessed for study eligibility by the Investigator or Coordinator. All the inclusion criteria must be met and none of the exclusion criteria may apply. All the results from the screening procedures must be available before determining a subject's eligibility for the study.

The following procedures will be performed at the screening visit:

- Obtain written informed consent (if not already obtained)
- Subject Identification Number assigned
- Inclusion/exclusion criteria review
- Medical history review
- Demographics
- Review concomitant medication usage
- Obtain vital sign measurements (Height, weight, blood pressure, body mass index, pulse, respiratory rate, temperature, waist circumference)
- Obtain blood sample for laboratory testing (Total testosterone levels, free testosterone levels, IGF-1, PSA, fasting glucose, comprehensive metabolic panel, CK, lipid profile, HGA1c, fasting insulin level, TSH, and Free T4 levels, lutenizing hormone, FSH, CBC, CRP)
- Urinalysis
- Physical Exam
- 6 Minute Walk Test
- International Prostate Symptom Score
- Rectal exam
- Electrocardiogram (EKG)

6.2.2 Baseline Evaluations

The following procedures will be performed at the baseline visit:

- Enrollment of subject into study
- Conduct final review of eligibility
- Quantitative Muscle Testing
- Manual Muscle Testing
- FSHD Clinical Outcome Measure (FSHD-COM)
- Forced Vital Capacity
- FSHD-Health Index (FSHD-HI)
- PROMIS-57
- Beck Depression Inventory (BDI)
- Epworth Sleepiness Scale
- Fatigue Severity Scale
- Dual Energy X-Ray Absorptiometry (DEXA)
- Fundoscopic exam
- Laboratory studies (if not done within 7 days as part of the screening visit)
- Quantitative Insulin Sensitivity Check Index
- Side Effect Questionnaire
- International Physical Activity Questionnaire
- Instruct subject about correct administration of study drug
- Administration of first dosage of each therapy

Both study drugs will be administered after all screening procedures have been completed and eligibility has been determined. Testosterone and rHGH will be administered at time points separated by greater than one hour. This time is sufficient to identify any immediate site reaction related to either study medication. Both medications have been extensively studied in humans and the likelihood of any significant reaction is low. The following activities will also occur

- Obtain vital signs (blood pressure, pulse, respiratory rate, temperature)
- Inquire about any immediate side effects (e.g., nausea, dizziness, GI discomfort)
- Instruct subjects to bring unused study drug to each study visit, and to immediately report any adverse events to the investigator or coordinator.

6.3 Follow Up Visits

After the subject has completed the Screening/Baseline Visit, they will return to the Clinical Research Center for an in-person visit at 8 weeks, 16 weeks, and 24 weeks, and 36 weeks (after 12 weeks of washout). Subjects will also be contacted weekly to inquire about their general status and resolve any study medication issues. The in-person visits will take about 6 hours.

6.3.1 On-site Follow up Evaluations

The following activities will be completed during the on-site follow up visits. These visits may be conducted within $\pm$ 7 days of the target date. The last study visit while on drug (the 24 week visit) will be conducted before the 24 week has expired while the patient is still on study medication.

Week 8 Visit

An in-person visit at Week 8 will involve:

- Blood specimen for clinical safety (total testosterone levels, free testosterone levels, IGF-1, PSA, fasting glucose, comprehensive metabolic panel, CK, lipid profile, HGA1c, fasting insulin level, TSH, and Free T4 levels, LH, FSH, CBC, CRP)
- Urinalysis
- Quantitative Muscle Testing
- Manual Muscle Testing
- FSHD Clinical Outcome Measure (FSHD-COM)
- Forced Vital Capacity
- FSHD-Health Index (FSHD-HI)
- PROMIS-57
- Beck Depression Inventory (BDI)
- Epworth Sleepiness Scale
- Fatigue Severity Scale
- Vital signs (Height, weight, blood pressure, body mass index, pulse, respiratory rate, temperature, waist circumference)
- Fundoscopic exam
- Physical exam
- Rectal exam
- International Prostate Symptoms Score
- Quantitative Insulin Sensitivity Check Index
- Side effect questionnaire
- International Physical Activity Questionnaire
- Domain Delta
- EKG
- Review of concomitant medications and adverse events
- Exercise log review

Participants with no clinically significant adverse events or lab abnormalities will remain on their daily dosage of study medication.

Week 16 Visit
An in-person visit at Week 16 will involve:

- Blood specimen for clinical safety (Total testosterone levels, free testosterone levels, IGF-1, PSA, fasting glucose, comprehensive metabolic panel, CK, lipid profile, HGA1c, fasting insulin level, TSH, and Free T4 levels, LH, FSH, CBC, CRP)
- Urinalysis
- Quantitative Muscle Testing
- Manual Muscle Testing
- FSHD Clinical Outcome Measure (FSHD-COM)
- Forced Vital Capacity
- FSHD-Health Index (FSHD-HI)
- PROMIS-57
- Beck Depression Inventory (BDI)
- Epworth Sleepiness Scale
- Fatigue Severity Scale
- Dual Energy X-Ray Absorptiometry (DEXA)
- Vital signs (Height, weight, blood pressure, body mass index, pulse, respiratory rate, temperature, waist circumference)
- Fundoscopic exam
- Physical exam
- Rectal exam
- International Prostate Symptoms Score
- Quantitative Insulin Sensitivity Check Index
- Side effect questionnaire
- International Physical Activity Questionnaire
- Domain Delta
- EKG
- Review of concomitant medications and adverse events
- Exercise log review

Those participants with no clinically significant adverse events or lab abnormalities will remain on their daily dosage of study medication.

Week 24 Visit
An in-person visit at Week 24 will involve:

- Blood specimen for clinical safety (Total testosterone levels, free testosterone levels, IGF-1, PSA, fasting glucose, comprehensive metabolic panel, CK, lipid profile, HGA1c, fasting insulin level, TSH, and Free T4 levels, LH, FSH, CBC, CRP)
- Urinalysis
- Quantitative Muscle Testing
- Manual Muscle Testing
- FSHD Clinical Outcome Measure (FSHD-COM)
- Forced Vital Capacity
- FSHD-Health Index (FSHD-HI)
- PROMIS-57
- Beck Depression Inventory (BDI)
- Epworth Sleepiness Scale
- Fatigue Severity Scale

- Dual Energy X-Ray Absorptiometry (DEXA)
- Vital signs (Height, weight, blood pressure, body mass index, pulse, respiratory rate, temperature, waist circumference)
- Fundoscopic exam
- Physical exam
- Rectal exam
- International Prostate Symptoms Score
- Domain Delta
- Quantitative Insulin Sensitivity Check Index
- side effect questionnaire
- International Physical Activity Questionnaire
- EKG
- Review of concomitant medications and adverse events
- Exercise log review

After this visit, participants will go off of study medication.

Week 36 Visit (12 weeks after washout)
An in-person visit at Week 36 will involve:

- Blood specimen for clinical safety (Total testosterone levels, free testosterone levels, IGF-1, PSA, fasting glucose, comprehensive metabolic panel, CK, lipid profile, HGA1c, fasting insulin level, TSH, and Free T4 levels, LH, FSH, CBC, CRP)
- Urinalysis
- Quantitative Muscle Testing
- Manual Muscle Testing
- FSHD Clinical Outcome Measure (FSHD-COM)
- Forced Vital Capacity
- FSHD-Health Index (FSHD-HI)
- PROMIS-57
- Beck Depression Inventory (BDI)
- Epworth Sleepiness Scale
- Fatigue Severity Scale
- Dual Energy X-Ray Absorptiometry (DEXA)
- Vital signs (Height, weight, blood pressure, body mass index, pulse, respiratory rate, temperature, waist circumference)
- Fundoscopic exam
- Physical exam
- Rectal exam
- International Prostate Symptoms Score
- Quantitative Insulin Sensitivity Check Index
- Side effect questionnaire
- International Physical Activity Questionnaire
- Domain Delta
- EKG
- Review of concomitant medications and adverse events
- Exercise log review

6.3.2 Telephone-based Follow up Evaluations

Participants will receive a weekly phone call to evaluate for any side effects or interval changes in medical health. Each participant will be asked if they have any questions regarding the study or the study medications.

Participants will be asked if they have been compliant with the study medications. Reasons for non-compliance will be discussed as will scheduling for upcoming in-person assessments.

6.4 Unscheduled Visits

Unscheduled in-person visits may occur at any time during the study. Assessments listed below will be completed and any data generated, including that from unscheduled telephone contacts, should be documented on appropriate study evaluation forms. These evaluations may take place at the Clinical Research Center:

- Vital signs (Height, weight, blood pressure, body mass index, pulse, respiratory rate, temperature, waist circumference)
- Specimen collection for safety laboratory tests (if deemed necessary by the site Investigator to assess adverse events)
- Assessment of adverse events
- Review of concomitant medications
- Assessment of study drug compliance

If a subject has an Unscheduled Visit between the scheduled visits he/she should be instructed to attend his/her next visit according to the study schedule as planned.

6.5 Premature Discontinuation of Study Drug

In the event of adverse events, non-compliance, protocol violation, intolerability, or other safety reason there may be a need for a premature discontinuation of study drug. Subjects will be allowed to permanently discontinue study drug but still be followed in the study per the intent-to-treat principle. If a subject prematurely discontinues study drug, the reason for discontinuation will be recorded. Protocol assessments should be conducted per the schedule of activities for subjects who continue to be followed off study drug. A participant who has discontinued study drug will be sent postage and shipping materials to return the remainder of their study medication. This medication will be destroyed and not used in another study participant.

6.6 Premature Withdrawal from the Study

In the event a subject is unwilling or unable to continue to be followed off study drug, when possible, a complete final evaluation using the Premature Withdrawal visit assessments will be conducted (if the subject is willing) and all unused study drug returned to the site coordinator:

- Blood specimen for clinical safety (Total testosterone levels, free testosterone levels, IGF-1, PSA, fasting glucose, comprehensive metabolic panel, CK, lipid profile, HGA1c, fasting insulin level, TSH, and Free T4 levels, LH, FSH, CBC, CRP)
- Urinalysis
- Quantitative Muscle Testing
- Manual Muscle Testing
- FSHD Clinical Outcome Measure (FSHD-COM)
- Forced Vital Capacity
- FSHD-Health Index (FSHD-HI)
- PROMIS-57
- Beck Depression Inventory (BDI)
- Epworth Sleepiness Scale
- Vital signs (Height, weight, blood pressure, body mass index, pulse, respiratory rate, temperature, waist circumference)
- Fundoscopic exam
- Physical exam
- Rectal exam
- Prostate symptom scale

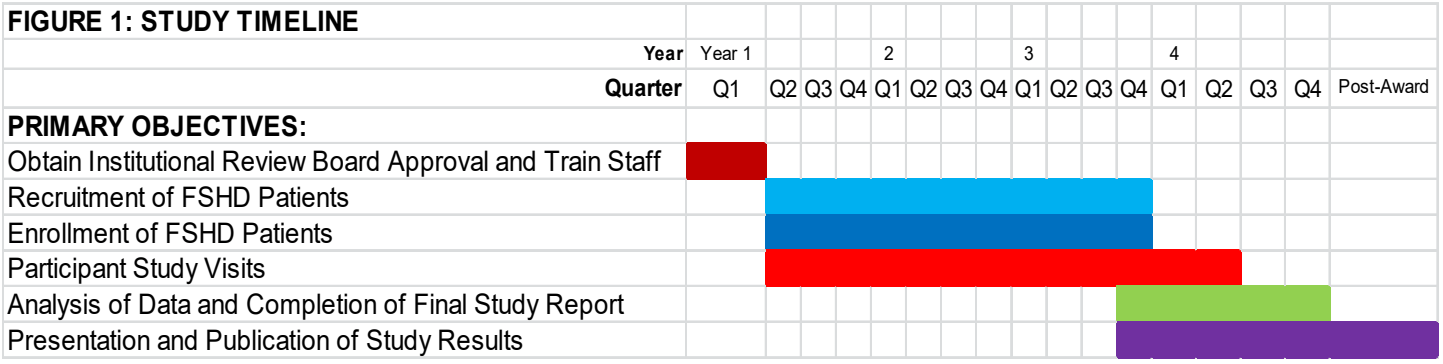
- International Prostate Symptoms Score
- Quantitative Insulin Sensitivity Check Index
- Side effect questionnaire
- International Physical Activity Questionnaire
- Domain Delta
- EKG
- Review of concomitant medications and adverse events
- Exercise log review

If a subject does not return for an in-person evaluation, adverse events, concomitant medications, reason for withdrawal and method of study drug return will be reviewed by phone when possible and the conclusion of study participation page will be completed.

6.7 Milestones and Study Calendar

We will obtain local IRB approval and train all clinical site staff in quarter 1 of year 1 (Q1Y1); enroll our first patient by Q2Y1; have 25% of participants enrolled by Q4Y1; 50% by Q3Y2; 75% by Q2Y3; and 100% by Q1Y4. We will complete all data collection by Q3Y4 and complete our study analysis and final NIH study report by Q4Y4 (See figure below).

FIGURE 1: STUDY TIMELINE



A planned enrollment table is provided below

STARFiSH Enrollment Timeline (Estimated)

	Visit	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR
Year 1 (2017-2018)	Screening				1		2	3		4		5	6
	Baseline				1		2	3		4		5	6
	Week 8					1		2	3		4		5
	Week 16							1		2	3		4
	Week 24									1		2	3
	Week 36												1
	Visit	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR
Year 2 (2018-2019)	Screening		7		8	9		10		11	12		13
	Baseline		7		8	9		10		11	12		13
	Week 8	6		7		8	9		10		11	12	
	Week 16		5	6		7		8	9		10		11
	Week 24		4		5	6		7		8	9		10
	Week 36		2	3		4		5	6		7		8
	Visit	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR
Year 3 (2019-2020)	Screening		14	15		16		17	18	19	20		
	Baseline		14	15		16		17	18	19	20		
	Week 8	13		14	15		16		17	18	19	20	
	Week 16	12		13		14	15		16		17	18	19
	Week 24		11	12		13		14	15		16		17
	Week 36	9		10		11	12		13		14	15	
	Visit	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR
Year 4 (2020-2021)	Screening												
	Baseline												
	Week 8												
	Week 16	20											
	Week 24	18	19	20									
	Week 36	16		17	18	19	20						

	Y1	Y2	Y3	Y4
Screening	6	7	7	0
Baseline	6	7	7	0
Week 8	5	7	8	0
Week 16	4	7	8	1
Week 24	3	7	7	3
Week 36	1	7	7	5
Total Visits	25	42	44	9

7.0 ASSESSMENTS & OTHER EVALUATIONS

7.1 Efficacy Assessments

7.1.1 Neuromuscular Assessments

6 Minute Walk Test: The six minute walk test (6MWT) measure has been extensively studied and utilized in neuromuscular populations[36-38]. It represents patient function and one of the most prevalent issues that impairs FSHD quality-of-life.[39,40]

Quantitative Muscle Testing (QMT): Maximum Voluntary Isometric Contraction Testing of the limb muscles will be performed using the Quantitative Muscle Assessment (QMA) system. This system uses an adjustable cuff to attach the patient's arm or leg to an inelastic strap that is connected to a force transducer with a load of 0.5 to 1,000 Newtons. Measurements resulting from this method of strength testing have been used for several neuromuscular diseases. [8,41-43] Six selected muscle groups will be tested bilaterally (biceps, triceps, quadriceps, hamstrings, handgrip, shoulder external rotators). These particular muscles were chosen because they show excellent test-retest reliability in neuromuscular patients and normal volunteers and they reflect affected muscle groups in FSHD amenable to therapeutic intervention.[8] A composite QMT score will be generated by expressing each muscle strength score as a percent of predicted normal given the subject's age, gender, and height and averaging across muscles.[8,44] Additional analysis of QMT strength will include absolute strength analysis, and analysis of upper and lower limb strength individually.

Manual Muscle Testing (MMT): Manual muscle testing will be performed on 34 muscle groups (bilateral shoulder abductors, shoulder external rotators, elbow flexors, wrist flexors, wrist extensors, hip flexors, hip abductors, knee extensors, hip extensors, knee flexors, hip adductors, elbow extensors, ankle dorsiflexors, plantar flexors, common finger extensors, and thumb flexors, plus neck extensor and neck flexors). Measurements resulting from this method of strength testing have been utilized in prior clinical trials of musculoskeletal disease.[41,43,45,46]

The FSHD Clinical Outcome Measure (FSHD-COM): The FSHD-COM is an evaluator-administered test that measures multiple aspects of physical function known to be impaired in FSHD. Tests included in the FSHD-COM evaluate leg function, arm/shoulder function, trunk function, hand function, and balance. Leg function is evaluated using sit to stand times,[47] the six minute walk test,[36-38] self-selected gait speed,[48,49] time to go 30 feet,[50] and time to ascend stairs.[50] Arm and shoulder function are measured using range of motion determinations at the shoulders and elbows, [51] and the time it takes a participant to don and doff a coat.[52] Trunk function is measured using the time it takes a participant to pick up a penny from the floor,[52] sit up with the feet held, and go from a supine to sitting position. Hand function is measured using QMT grip strength determinations. Lastly, balance is approximated using the timed up and go test.[53] The composite FSHD-COM is currently being validated in our longitudinal study of 40 FSHD patients. Each of individual tests of the FSHD-COM (and the FSHD-COM total score) will be analyzed.

7.1.2 Functional Assessments

Forced Vital Capacity: Respiratory function will be measured using forced vital capacity.

Epworth Sleepiness Scale will be completed to estimate subject daytime sleepiness.

Fatigue Severity Scale will be completed to estimate subject fatigue.

Dual Energy X-Ray Absorptiometry (DEXA). Lean body mass (LBM) will be measured via Dual Energy X-Ray Absorptiometry (DEXA). DEXA provides a practical and effective approach to determine lean muscle mass, and has been extensively utilized in prior neuromuscular clinical trials.[54,55] Both total LBM and regional LBM will be measured.[56] DEXA measurement has multiple advantages over the more recently described and

debated MRI techniques. Specifically, compared to MRI, DEXA has a more extensive history of use, a more standardized analysis, is not as dependent on perfect participant positioning, and is more accessible, more affordable, and can be utilized in patients with metallic foreign bodies, aneurysm clips, pacemakers, claustrophobia, and metallic implants, and has a better correlation with change in six minute walk distances compared to MRI thigh measurements.[57,58] Most importantly, the use of DEXA as a biomarker is supported by a prior study of combination therapy where LBM increases (measured by DEXA) occurred prior to later observable marked improvements in patient strength and function.[59]

7.1.3 Self-reported Assessments

The FSHD-Health Index (FSHD-HI): The FSHD-HI is a disease-specific patient reported outcome measure designed to assess patient-relevant effects during therapeutic trials.[39,40] The instrument measures a patient's assessment of their: 1) Mobility; 2) Hand and arm function; 3) Emotional issues; 4) Cognitive impairment; 5) Decreased satisfaction in social situations; 6) Decreased performance in social situations; 7) Specific activity impairment; 8) Fatigue; 9) Pain; 10) Eating problems; 11) Communication difficulty; 12) Problems with shoulders and arms; 13) Weakness of the back, chest, or abdomen; and, 14) Body image and has been created to satisfy FDA recommendations for use in supporting drug labeling applications. The FSHD-HI is currently being validated in NIH sponsored longitudinal study of 40 FSHD patients at the University of Rochester.

PROMIS-57: The PROMIS-57 generates scores for depression, anxiety, fatigue, pain interference, pain intensity, physical function, sleep disturbance, and satisfaction with participation in social roles.[60]

Beck's Depression Inventory (BDI): The BDI is a widely used instrument for monitoring change in depressive symptoms.[61]

International Physical Activity Questionnaire (IPAQ)[62] will be completed at each visit. In addition, participants will complete a daily exercise log that we developed for FSHD patients in U01AR065119. This exercise log will highlight the type and duration of activities that the FSHD participate in on a daily basis.

7.2 Feasibility Assessments

Several outcome measures have been incorporated to evaluate recruitment and retention for this particular study. These include the subject's willingness to travel to Rochester, NY for a screening/baseline visit and the number of consented subjects. Information regarding retention will be captured by recording the number of completed study visits, the number of subjects that completed the study without drug discontinuation, and the number of subjects who completed the study. Whenever possible, reasons for refusal to participate will be recorded.

Compliance will be measured as the percentage of distributed packs and vials that were used out of those scheduled to be used. Additionally, the subjects will be asked whether or not they required assistance with administration of the study drug or if they were able to self-administer all doses.

7.3 Safety Assessments

7.3.1 Adverse Event Assessment

Adverse events, attribution of the adverse event to study drug, actions taken with respect to study drug (i.e. dosing changes), and classification of seriousness will be systematically documented. Serious adverse events (death, life-threatening adverse event, persistent or significant disability/incapacity, or subject hospitalization or prolongation of existing hospitalization) will be specifically noted and adjudicated for relationship to study drug.

7.3.2 Clinical Safety Laboratory Tests

Blood and urine samples will be obtained for clinical safety lab assessments (complete metabolic panel, complete blood count, and urinalysis) at each in-person visit as described in Sections 6.0. A centralized clinical research organization will manage laboratory specimen. The following clinical safety lab tests will be performed:

COMPREHENSIVE METABOLIC PANEL	COMPLETE BLOOD COUNT	HORMONE ANALYTES	Other Tests
Sodium (Na)	White Blood Cell Count (WBC)	Total testosterone	Total Cholesterol
Potassium (K)	Red Blood Cell Count (RBC)	Thyroid Stimulating Hormone	Low Density Lipoprotein Cholesterol
Chloride (Cl)	Hemoglobin (Hb)	Free T4	High Density Lipoprotein Cholesterol
Carbon Dioxide (CO2)	Hematocrit (HCT)	Luteinizing Hormone	Triglycerides
Blood Urea Nitrogen (BUN)	Mean Corpuscular Volume (MCV)	Follicle Stimulating Hormone	Non-HDL-C
Glucose	Mean Corpuscular Hemoglobin (MCH)	IGF-1	Cholesterol-HDL-C ratio
Calcium (Ca)	Mean Corpuscular Hemoglobin Concentration (MCHC)	Insulin (Fasted)	CK
Creatinine (Crn)	Red Blood Cell Distribution Width (RDW)	Free Testosterone	PSA
Bilirubin Total	MVP	HGA1c	
Albumin	Platelet Count (PLT)		
Protein (NOS) Total			
Glutamic-Oxaloacetic Transferase (AST, SGOT)			
Glutamic-Pyruvate Transferase (ALT, SGPT)			
Alkaline Phosphatase NOS			
CRP			

7.3.3 Treatment-specific Assessments

Subjects will be monitored for the following treatment-related events:

- peripheral edema
- carpal tunnel syndrome
- gynecomastia
- insulin resistance
- arthralgia
- increased erythropoiesis
- reduced HDL cholesterol
- elevated prostate specific antigen
- elevated blood pressure

Physical exams will be implemented to evaluate for peripheral edema, carpal tunnel symptoms, and joint pain, and will include a fundoscopic examination using a pan-optic ophthalmoscope. Participants will also be monitored with the International Prostate Symptom Scale[63], and the quantitative insulin sensitivity check index (Quicki) to evaluate for signs of prostate dysfunction or diabetes.[20,29] Patients will serially complete a treatment specific questionnaire at each study visit designed for early detection of adverse events associated with study drug and will be contacted on a weekly basis by study personnel to monitor for any adverse events.[28]

8.0 STATISTICAL CONSIDERATIONS

Statistical analysis of the study will be performed by the Department of Biostatistics and Computational Biology at the University of Rochester under the direction of the Primary Study Biostatistician, Dr Michael P. McDermott.

8.1 Analysis of Safety Outcomes: The primary measures of safety and tolerability will consist of: 1) the occurrence of any serious or non-serious adverse events; and, 2) the ability of participants to complete a 24-week period on combination therapy without having to discontinue either therapy. An adverse event will be defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment or procedures that may or may not be considered related to the medical treatment or procedure (ICH E-6 Guidelines for Good Clinical Practices). Stable chronic conditions that are present prior to the start of the study and do not worsen during the trial are not considered adverse events. Minor fluctuations in signs or symptoms of the disease under study are also not considered adverse events, but significant worsening of the disease beyond what is expected will be reported.
Adverse events are detected in two ways:
Clinical: Symptoms reported by the participant or signs detected on examination.
Ancillary Tests: Abnormalities of vital signs, EKG, laboratory tests, and other diagnostic procedures.

The research team (including the safety monitor and PI) will assess whether each adverse event is unexpected or related (or possibly related) to the study medication. The adverse event may be a new illness, a worsening of a sign or symptom of the condition under treatment, a worsening of concomitant illness, an effect of the study medication or a combination of these factors. Each event will be classified as mild, moderate, or severe and serious vs. non-serious based on preset rules. Participants will specifically be monitored for the following events that have been previously associated with treatment: peripheral edema, carpal tunnel syndrome, gynecomastia, insulin resistance, arthralgia, increased erythropoiesis, reduced HDL cholesterol, elevated prostate specific antigen, and elevated blood pressure. Physical exams will be implemented to evaluate for peripheral edema, carpal tunnel symptoms, and joint pain, and will include fundoscopic and rectal examinations. Participants will also be monitored with the International Prostate Symptom Scale46, and the quantitative insulin sensitivity check index (Quicki) to evaluate for signs of prostate dysfunction or diabetes. Patients will serially complete a treatment specific questionnaire at each study visit designed for early detection of adverse events associated with study drug and will be contacted on a weekly basis by study personnel to monitor for any adverse events.

The primary tolerability outcome variable is the ability to take combination study medication for 24 weeks and complete the 24 week treatment period. The criterion for declaring combination treatment well tolerated will be based on a hypothesis test that compares the observed tolerability rate against a tolerability rate that would be considered unacceptably low. We believe that 70% is a reasonable choice for the unacceptably low tolerability rate in this context. A test based on the binomial distribution will be performed for $H0: \pi \leq 0.70$ vs. $H1: \pi > 0.70$, where π is the true probability of tolerability. The decision rule will be to reject the null hypothesis of unacceptable tolerability if the number of subjects tolerating the dosage is 18 (out of 20) or greater. This rule will provide 80% power to detect that the dosage is tolerable (has a tolerability rate > 70%) if the true tolerability rate is 92%. The actual significance level of this test is 3.6%. Adverse events will be tabulated overall and by severity. For each adverse event, a 95% confidence interval will be computed for the incidence using the Wilson score method. This will be repeated excluding all mild symptoms. Similar analyses will be performed after grouping adverse events by body system. Individual adverse events will be listed, with

particular attention paid to serious adverse events. Laboratory tests, vital signs, and EKG abnormalities will be summarized similarly; continuous values may be analyzed using the methods described below for lean body mass. A complete accounting of subject disposition will be summarized, including a tabulation of subject withdrawals, dosage reductions, dosage suspensions, and early discontinuations of study medication (with reasons for each). Concomitant medication usage for each participant will be listed for review.

8.2 Analysis of Outcome Measures of Efficacy:

Analysis of Lean Body Mass: Lean body mass obtained using DEXA will be the objective primary marker used to determine whether combination treatment shows sufficient promise to consider further studies in FSHD. The analysis of this outcome will involve the use of a repeated measures analysis of variance model (i.e., the so-called “mixed model repeated measures”, or MMRM, analysis strategy81), with time (treated as a categorical variable) as the factor of interest. The covariance matrix for the within-subject observations will be modeled using an unstructured pattern. Ninety-five percent confidence intervals for mean changes from baseline to each visit will be computed using this model, with the 24-week time point being of primary interest. A test for significance of the mean change from baseline to 24 weeks will likewise be performed with this model using a significance level of 5% (two-tailed). The analyses will be performed according to the intention-to-treat principle and will include all enrolled participants. The repeated measures analysis of variance model to be used for these analyses uses a direct-likelihood approach to estimate the parameters of interest using all available data from all participants. A key assumption underlying this analysis is that the missing data are “missing at random” (MAR), i.e., the probability that the responses are missing for a subject depends only on the set of observed data for that subject and not on the specific missing values that were not obtained. The underlying assumptions of the statistical model (e.g., normality) will be thoroughly checked and remedial measures (e.g., transformations, use of non-parametric methods) may be necessary if serious violations of these assumptions are detected, but this is not expected for the lean body mass outcome based on our previous experience with its use in clinical trials of FSHD.40 A similar model that also includes amount of exercise (a dichotomous baseline variable based on exercise log data) and the interaction between amount of exercise and time will be used to explore differences between exercise subgroups with respect to changes in lean body mass after combination treatment.

Exploratory Analyses of Potential Efficacy: Outcome measures that will be used to explore potential efficacy include changes from baseline in the distance walked in 6 minutes, MVICT scores, FSHD-COM (total score and individual tests), FVC, Epworth Sleepiness Scale, Fatigue Severity Scale, FSHD-HI scores, PROMIS-57 scores, and BDI score. The analyses of these outcomes will be performed as above for lean body mass. It should be emphasized that these analyses will be considered to be purely exploratory, although the distance walked in 6 minutes will be given higher priority in terms of interpreting the potential functional benefit of combination treatment.

8.3 Analysis of Pharmacokinetic Outcomes: Changes from baseline in all serum markers will be summarized descriptively. Formal analyses of changes from baseline will also be performed using the methods described above for lean body mass.

8.4 Analyses for Feasibility

Measures of feasibility will be tabulated as part of our total data analysis. These measures will include:

1. Willingness to travel to Rochester, NY for a screening/baseline visit
2. Number of consented subjects
3. Number of completed rHGH injections per enrolled participant
4. Number of completed testosterone injections per enrolled participant
5. Ability of participants to administer study drug
6. Number of completed study visits per participant
7. Number of subjects that completed the study without drug discontinuation
8. Number of subjects who completed the study

8.5 Missing Data

A key assumption underlying this analysis is that the missing data are "missing at random" (MAR), i.e., the probability that the responses are missing for a subject depends only on the set of observed data for that subject and not on the specific missing values that were not obtained.[64]

8.6 Sample Size Considerations

The primary tolerability outcome variable is the ability to take combination study medication for 24 weeks and complete the 24 week treatment period. The criterion for declaring combination treatment well tolerated will be based on a hypothesis test that compares the observed tolerability rate against a tolerability rate that would be considered unacceptably low. We believe that 70% is a reasonable choice for the unacceptably low tolerability rate in this context. A test based on the binomial distribution will be performed for H0: $\pi \leq 0.70$ vs. H1: $\pi > 0.70$, where π is the true probability of tolerability. The decision rule will be to reject the null hypothesis of unacceptable tolerability if the number of subjects tolerating the dosage is 18 (out of 20) or greater. This rule will provide 80% power to detect that the dosage is tolerable (has a tolerability rate > 70%) if the true tolerability rate is 92%. The actual significance level of this test is 3.6%. The Table below provides information on the precision with which the incidence of a particular adverse event can be estimated as well as the probability of observing at least one such event during the trial given different values for the true incidence of the adverse event in the target FSHD population receiving combination therapy. A sample size of 20 participants will yield a 95% upper confidence bound for the incidence that is within approximately 20% of the observed incidence. It will also make it very likely that an adverse event with a true incidence ≥ 15% will be observed in at least one subject during the trial.

Observed Adverse Event Incidence	95% Upper Confidence Bound	True Adverse Event Incidence	Probability of Observing at Least 1 Adverse Event
5%	21.6%	5%	26.1%
10%	28.3%	10%	60.8%
15%	34.4%	15%	82.4%
20%	40.1%	20%	93.1%
25%	45.6%	25%	98.0%
30%	50.8%	30%	99.2%

For lean body mass, an estimated standard deviation of 1.6 kg was derived using data on 24-week change from participants in our ongoing longitudinal study of FSHD progression (PI: Heatwole, U01AR065119). Assuming a standard deviation of 1.6 kg meters for the this outcome variable, a sample size of 18 participants will provide 85% power to detect a mean change of 1.2 kg , using a t-test and a 5% significance level (two-tailed). A sample size of 20 participants will allow for an anticipated attrition rate of 10%.

For the 6MWT, an estimated standard deviation of 42.3 meters was derived using data on 24-week change from participants in our ongoing longitudinal study of FSHD progression. Assuming a standard deviation of 40 meters for this outcome variable, a sample size of 18 participants will provide 85% power to detect a mean change of 30 meters, using a t-test and a 5% significance level (two-tailed). Recent studies in chronic obstructive pulmonary disease, coronary artery disease, and Duchenne muscular dystrophy support a distance of 25-35 meters as representing a minimal clinically important change. A sample size of 20 participants will allow for an anticipated attrition rate of 10%.

8.7 Data and Safety Monitoring

Participants will be monitored in accordance with current Endocrine Society Guidelines.[18] The independent medical safety monitor (Dr. Emma Ciafaloni) is a board certified physician with knowledge of both FSHD and endocrine therapies. In addition to the PI, the safety monitor will directly review all laboratory values, vital signs, EKG results (e.g., PR, QRS, and corrected QT intervals, rhythm, conduction, and waveform analysis),

adverse events, and all other safety related data on a quarterly basis. Any safety concerns identified by the PI will be addressed by the safety monitor in real time. The safety monitor will have the final determination if any medication needs to be stopped or reduced or if a participant needs to be withdrawn from the study. Our study endocrinologists (Dr. Bhasin and Dr. Weber), the study cardiologist (Dr. Rosero), and the study urologist (Dr. Rashid) will also assist with any questions throughout the study. If an adverse event occurs, the safety monitor will have the option to reduce one or both of the medications by 25%, 50%, 75%, or 100% based on the type of adverse event noted and if it was attributed to rHGH and/or testosterone. Elevations of IGF-1 higher than 400 ng/mL, a total testosterone level higher that 1100 ng/dL or a HCT ≥54% will warrant study medication reduction.[20] One of our endocrinologist consultants, Dr. Bhasin, has written protocols for the safe adjustment of testosterone supplementation and will advise on each individual case in whom elevated levels are noted.[65] The report of any serious adverse event will comply with both FDA and IRB requirements. All participants will be followed and evaluated as scheduled (as they are willing) regardless of the dosages of the study medications.

Testosterone enanthate and rHGH are both approved therapeutics for use in human populations. We will carefully monitor for all potential adverse events associated with these therapies throughout the study. In rHGH, reported side effects include: peripheral edema, carpal tunnel syndrome, gynecomastia, insulin resistance, papilledema, and arthralgia. Although stimulation of existing carcinomas with rHGH has been hypothesized, no evidence has yet been produced to support this hypothesis.[10,66] For testosterone, reported side effects include: erythropoiesis (increased hematocrit), reduction in HDL cholesterol, elevation in prostate specific antigen, worsening of sleep apnea, and elevation in blood pressure. In men over 65, there may be a higher risk of cardiovascular events associated with testosterone use.[67] Higher rates of adverse events have been claimed in Veterans Affairs patients receiving testosterone after coronary angiography; however these results have been refuted.[68,69] In contrast, other studies have demonstrated that mortality rates are higher in patients with a deficiency of testosterone compared to those treated with testosterone[70,71], and that testosterone is not associated with any cardiovascular risk.[72,73,74,75] There are no data to suggest that FSHD patients will experience any disease-specific side effects that have not previously been identified in studies involving healthy adults. Regardless, as a precaution, FSHD patients over the age of 65 and those with known coronary artery disease will not be included in this study. In addition, we will serially monitor CK and CRP levels to evaluate for any unexpected evidence of increasing muscle inflammation. Cosmetic side effects may occur with testosterone use and include hirsutism, acne, voice changes, gynecomastia and alopecia. While there is no evidence to support a causative role in prostate cancer in men, androgens may enlarge an occult prostate tumor that has androgen sensitivity.[10,76] No patients with known prostate cancer will be enrolled, and all men will be screened for signs of prostate change throughout their involvement. Prior trials of combination therapy have not observed significant adverse events that have not been observed with single agent approaches.[20,28,29] In the majority of cases, the adverse events observed with combination therapy during prior clinical trials were mild and responsive to medication dosage reductions.[20,28,29]

Patients will be monitored for suicide risk through use of the Beck Depression Inventory and safety measures will be taken to mitigate risk if a patient discloses suicidal thoughts. A standard operating procedure for safety triage is in place to assess and address the patient's safety. The patient will be connected with care if needed and continuously monitored.

9.0 ADVERSE EVENT REPORTING, MONITORING & REPORTABLE EVENTS

9.1 Definition of an Adverse Event

An adverse event is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment or procedures that may or may not be considered related to the medical treatment or procedure (ICH E-6 Guidelines for Good Clinical Practices). Stable chronic conditions that are present prior to the start of the study and do not worsen during the trial are not considered adverse events. Minor fluctuations in signs or symptoms of the disease under study are also not considered adverse events, but significant worsening of the disease should be reported.

Adverse events are detected in two ways:
Clinical: Symptoms reported by the subject or signs detected on examination
Ancillary Tests: Abnormalities of vital signs, EKG, lab tests, and other diagnostic procedures.

Adverse events are typically associated with physical or psychological, rather than social or economic harm. The investigator must assess whether the adverse event is unexpected and related (or possibly related). The adverse event may be a new illness, a worsening of a sign or symptom of the condition under treatment, a worsening of concomitant illness, and an effect of the study medication or a combination of these factors. Planned surgical procedures for pre-existing conditions are not adverse events.

9.1.1 Classification
Adverse events are to be classified by the investigator as serious or non-serious.

9.1.2 Grade of Intensity
The maximum intensity of an adverse event will be graded as follows:

GRADE LEVEL	DEFINITION
1	Mild (awareness of a sign or symptom that is easily tolerated)
2	Moderate (sign or symptom intense enough to interfere with usual activity)
3	Severe (interferes significantly with ability to do work or usual activity)

9.1.3 Relationship to Study Drug
With careful medical consideration at the time of evaluation, the reasonable possibility of an adverse event's relationship to study medication is to be assessed. The Safety Monitor's opinion may be sought in those cases in which the site investigator is unable to make an independent judgment. The Safety Monitor may in turn consult with the principal investigator as needed. The following definitions are general guidelines only to help assign grade of attribution:

GRADE LEVEL	DESCRIPTOR	DEFINITION
1	Unrelated	Adverse event is clearly not related to the investigational drug (s)
2	Unlikely	Adverse event is doubtfully related to the investigational drug (s)
3	Possible	Adverse event may be related to the investigational drug (s)
4	Probable	Adverse event is likely related to the investigational drug (s)
5	Definite	Adverse event is clearly related to the investigational drug (s)

Definite
This category applies to those adverse events, which after careful medical consideration at the time they are evaluated, are felt with certainty to be related to study medication.

An adverse event may be considered definitely related if or when (at least three of the following):
- It follows a direct temporal sequence from administration of the study medication.
- It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject.
- It disappears or decreases on cessation or reduction in dosage. There are important exceptions when an adverse event does not disappear upon the discontinuation of study medication, yet drug-relatedness clearly exists.
- It follows a known pattern of response to the test drug.

Probable
This category applies to those adverse events, which after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be likely related to study medication.

An adverse event may be considered probably related if or when (at least three of the following):
- It follows a reasonable temporal sequence from administration of the study medication.
- It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject.
- It disappears or decreases on cessation or reduction in dosage. There are important exceptions when an adverse event does not disappear upon the discontinuation of study medication, yet drug-relatedness clearly exists.
- It follows a known pattern of response to the test drug.

Possible
This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, a connection with administration of study medication appears unlikely but cannot be ruled out with certainty.

An adverse event may be considered possibly related if or when (at least two of the following):
- It follows a reasonable temporal sequence from administration of the study medication.
- It could not readily have been produced by the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject.
- It follows a known pattern of response to the test drug.

Unlikely
In general, this category can be considered applicable to those adverse events, which, after careful medical consideration at the time they are evaluated, are judged to be doubtfully related to study medication.

An adverse event may be considered unlikely related if or when (must have two):
- It does not follow a reasonable temporal sequence from the administration of the test drug.
- It could readily have been produced by the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject.
- It does not follow a known pattern of response to the test drug.
- It does not reappear or worsen when the drug is re-administered.

Unrelated
In general, this category can be considered applicable to those adverse events, which, after careful medical consideration at the time they are evaluated, are judged to be clearly unrelated to study medication.

An adverse event may be considered unrelated if or when (must have three):
- It does not follow the temporal sequence from the administration of the test drug.
- It was most likely produced by the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject.
- It does not follow a known pattern of response to the test drug.
- It does not reappear or worsen when the drug is re-administered.

9.1.4 Adverse Event Assessment
At each in-person visit and telephone contacts, occurrence of adverse events will be assessed by verbally asking subjects if they have had any problems or symptoms since their last visit.

If the subject reports an adverse event, the investigator/coordinator will probe further to determine:
- Time of onset and resolution
- Frequency
- Causality/relation to study treatment
- Intensity

- Action taken regarding study medication
- Outcome

9.1.5 Reporting of Adverse Events

Adverse events encompass both physical and psychological harms. During the clinical trial, all adverse events encountered must be reported on the Adverse Event log, whether considered to be related to study medication or not. Adverse events must be evaluated by the site investigator for seriousness and causality prior to entry on the electronic Case Report Form (eCRF). All recorded adverse events should be evaluated at each subsequent visit until the condition has resolved or until the site investigator and/or Safety Monitor agree that the condition no longer needs to be followed. At every visit the investigator must review the adverse events with the subject and record any new changes in status or events since the last visit.

9.1.6 Follow-Up of Adverse Events at Permanent Withdrawal or End of Study

Adverse events ongoing at the time of a subject's withdrawal from or completion of the study must be followed for 30 days or until the investigator deems the condition has resolved or the condition has stabilized (whichever occurs first).

9.2 Definition of Serious Adverse Event (SAE)

Any untoward medical occurrence (adverse event) that at any dosage:

- results in death;
- is life-threatening event (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- results in congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g. allergic bronchospasm requiring intensive treatment in the emergency room or at home, convulsions not resulting in inpatient hospitalization, development of drug dependency or drug abuse, etc).

9.2.1 Reporting Serious Adverse Events

Responsibilities for reporting serious adverse events is outlined below:

- The Investigator or Coordinator should record all serious adverse events that occur during the study period (commencing once informed consent has been provided) on the Adverse Event log and in the appropriate source documents.

- Study Period: For the purposes of reporting serious adverse events, the study period is defined as the time period from when the subject signs the informed consent until 30 days following the subject's completion of the study.

- The following information should be supplied if available at the time of the telephone call: study name, site number, subject number, and age, gender, start date of study drug, whether study drug has been discontinued, date of randomization, date of last study drug dosage, date of onset of event, event description, whether event required treatment, death and autopsy report (if available), an identification of which criteria for a serious event have been met, and the Investigator's current opinion of the relationship between the event and the study drug or study participation.

- The Investigator and Coordinator will complete the MedWatch Form and update the AE, concomitant medications and dose management logs within 24 hours. The MedWatch form must be completed for all Serious Adverse Events regardless of causality or expectedness.

9.2.2 Monitoring of Serious Adverse Events

Adverse events are assessed by the study staff at each visit by recording all complaints of subjects and by assessment of the clinical features and surveillance labs. The progress of each SAE will be followed by the Investigator until resolution or until an appropriate endpoint is reached (resolution or determination of event to be chronic and/or stabilized).

9.3 Reportable Events (Incidents)

The following incidents will be considered reportable events and will be reported to the Independent Safety Monitor, the Investigator, and the IRB within 24 hours of the event, or the Investigator's knowledge of the event.

- Dosage suspension
- Dosage rechallenge
- Subject withdrawal
- Early discontinuation of study drug
- Serious adverse event (SAE)
- Suicide attempt
- Emergency treatment disclosure
- Clinically significant overdosage

9.4 RISK/BENEFIT ASSESSMENT

9.5 Potential Risks

Completion of patient-reported outcome measures may cause feelings of distress.

Muscle strength and function testing may cause bruising or temporary muscle soreness. For bedside respiratory testing, subjects may have difficulty breathing or may feel fatigued.

Patients may experience minor discomfort during the DEXA scan from lying in the same position for about 15 minutes. The amount of radiation exposure during the DEXA scans is relatively small. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (cellular abnormalities) or cancer. Patients' risk of radiation-related injury depends on their total lifetime exposure, not just the radiation dose received in this study.

Blood draws may cause pain, redness, bruising or infection at the site of the needle stick. Rarely some people feel lightheaded or faint.

Electrocardiogram (ECG/EKG) testing may cause minor skin irritation from the electrodes.

During the rectal examination, patients may feel some discomfort or pain, especially if the prostate gland is swollen or irritated. This pressure may make patients feel the need to urinate. A small amount of bleeding from the rectum may occur after an examination, especially if hemorrhoids or anal fissures are present. In rare cases, patients may feel lightheaded and faint.

The light of the ophthalmoscope during the funduscopic examination can cause some discomfort.

There is a potential for invasion of privacy or breach in confidentiality in this study.

The study team may be notified if patients receive other health care services at URMC or its Affiliates (e.g., visit to the emergency room). In addition, the following individuals may be informed of the patient's participation in research and may see results of testing conducted for this study:

- Staff at the University of Rochester Medical Center and its Affiliates (e.g., Strong Memorial Hospital, Highland Hospital, URMC primary care, specialist physician offices) who have a reason to access the patient's electronic health record.

- Individuals who request a copy of information from the patient's health record for activities such as treatment or payment (e.g., medical insurance companies, worker's compensation).

Risks of Testosterone:

Central Nervous System:	**Genitourinary:**	**Hematologic & Oncologic:**	**Cardiovascular:**
Irritability or aggressive behavior	Large prostate or prostate cancer	Deep vein thrombosis and pulmonary embolism (blood clots in veins or the lungs)	Major heart problems including stroke and heart attack (inconclusive data)
Altered taste or sense of smell	Inflammation of the prostate	Decreased white blood cells	Hypertension
Sleep apnea or worsening sleep apnea	Prostate lab abnormalities	Prostate problems including inflammation, cancer, nodules	Increased blood pressure
Insomnia	Changes in muscle bulk, body hair, and voice	Increase in the volume of red blood cells	Change in lipid profile (e.g., cholesterol and triglycerides)
Mood swings	Abnormal thyroid function	Increased hemoglobin in the blood	Swelling
Headache	Ejaculatory disorder	Bleeding	Widening of blood vessels
Fatigue	Problems urinating	Increased blood cells	Blood clots
Suicidal ideation	Testicular atrophy	Liver inflammation or cancer	**Dermatologic:**
Abnormal dreams	Increased spontaneity or frequency and duration of erections	Anemia (decrease in red blood cells or hemoglobin in the blood)	Rash or skin reaction at the injection site
Amnesia	Erectile dysfunction	**Neuromuscular & Skeletal:**	Increased body hair
Anxiety	Urinary tract infections	Arthralgia	Increased sweating
Depression	Reduced sperm levels	Back pain	Baldness
Personality changes	Excessive sexual stimulation	Pain at the injection site	Acne
Seizure	Yellow skin	Weakness	**Respiratory:**
Vision changes	Abnormal liver function, liver failure or cancer	Bleeding into joint space	Upper respiratory tract infection
Voice changes	Increased bilirubin in the blood or jaundice	Accelerated bone growth	Cold symptoms
Endocrine/ Metabolic:	**Gastrointestinal:**	Carpal tunnel syndrome	Shortness of breath
Hot flashes	Vomiting	restlessness	Bronchitis
Increased calcium in the blood	Heartburn	**Other:**	Sinus infection
Increased plasma estradiol concentration	Diarrhea	Increased tearing	
Weight gain	Increased appetite	Increased urination	
Gynecomastia (increased breast size)	Nausea	Allergic reaction	
	Gastrointestinal hemorrhage or	Testosterone abuse	

	irritation		

Other serious side effects, while very rare, may include: anaphylaxis (shock) reactions, congestive heart failure, or other life-threatening cardiovascular events.

While testosterone has not been shown to be a cause of cancer in humans, it is not recommended in patients with an active malignancy. In addition, testosterone may be associated with increase cardiovascular events in patients older than 65 and those with preexisting cardiac, kidney, or liver disease.

Risks of rHGH:

Endocrine & Metabolic	**Dermatologic:**	**Other:**
Dehydration	Sweating	Acute Critical Illness
Insulin resistance	Skin rash	Infection
Adrenal insufficiency	Acne	Candidiasis (yeast infection)
Hypothyroidism	Psoriasis (patches of abnormal skin)	Allergic reaction
High blood sugar	Hair loss	Intracranial Hypertension
Impaired glucose tolerance and diabetes mellitus	Increased growth of pre-existing moles	Abnormal tissue growth or tumor
Reduced serum cortisol levels	Loss of fat at the injection site	Papilledema
Central Nervous System:	**Gastrointestinal:**	Damage to the retinas of the eyes
Pain	Inflammation of the pancreas	Enlargement of facial features
Reduced skin sensation	Nausea	**Respiratory:**
Headache	Flatulence	Cough
Discomfort	Abdominal Pain	Rhinitis
Reduced sensation or numbness	Vomiting	Pharyngitis (inflammation of the back of the throat)
Dizziness	Gastritis	Flu-like symptoms
Depression	**Neuromuscular and Skeletal:**	**Cardiovascular:**
Fatigue	Joint pain	High blood pressure
Insomnia	Joint disease	Swelling
Seizure	Muscle pain or stiffness	Chest pain
Aggressive behavior	Fracture through the growth plate	
Otic:	Limb pain	
Ear infection or inflammation	Scoliosis	
Ear disease	Carpal tunnel syndrome	
Altered hearing	Weakness	

While rHGH has not been shown to be a cause of cancer in humans, it is not recommended in patients with an active malignancy.

9.6 Protection Against Risks

Study personnel are trained to minimize the risks associated with participation in this trial. Patients will be closely monitored and may withdraw from the study or any procedure at any time for any reason. Subjects may be referred for treatment, counseling or other necessary follow-up if needed. Any additional treatment, counseling, or follow-up may be provided by the patient or his insurance.

Safety measures will be taken to mitigate suicide risk if a patient discloses suicidal thoughts. A standard operating procedure for safety triage is in place to assess and address the patient's safety. The patient will be connected with care if needed and continuously monitored.

All study staff are fully trained in testing techniques and will ask patients how they are feeling throughout the course of the visit. Patients will be asked to report any concerns to study staff immediately.

To minimize the risk of invasion of privacy or breach in confidentiality, patients' data is labelled with a study number. All data will be stored in a secure manner and only study team members will have access to it.

Patients will not be eligible to participate in this study if they have any preexisting history of cancer, are known to have cancer, are older than 65 years old or have preexisting cardiac, kidney, or liver disease due to the risks of these patients receiving rHGH and/or testosterone.

Patients will be provided with the "label" information for both testosterone and rHGH to review and discuss with study staff. The study team will monitor for side effects during phone calls with patients every week and at each study visit. Patients will be asked to report to the study team if any adverse events occur.

9.7 Potential Benefits to Subjects
Patients may not benefit from participation in this research study. A potential benefit might be some improvement in muscle strength.

9.8 Alternatives to Participation
Patients do not have to participate in this study to receive care for FSHD. Testosterone and rHGH are FDA approved drugs and can be prescribed by physicians outside of the study.

10.0 ETHICS

10.1 Guidelines for Good Clinical Practices
Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible (*ICH E-6 Guideline for GCP*). The Principal Investigator will ensure that this trial is conducted in full accordance with the ethical principles which have their origin in the Declaration of Helsinki or with the laws and regulations of the country in which the research is conducted, whichever affords greater protection to the individual. The Principal Investigator will ensure that all individuals assisting with the trial are adequately qualified, informed about the protocol, any amendments to either the protocol, treatment or study procedures, and their trial-related duties and functions.

10.2 Informed Consent
The consent form will describe the purpose of the study, procedures to be followed, and risks and benefits of participation. The consent form document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations (i.e. HIPAA compliance). The document must be in a language understandable to the subject and must specify who informed the subject. Before being enrolled in the clinical study, subjects must consent to participate after the nature, scope and possible consequences of the clinical study have been explained in a form understandable to them. After reading the informed consent document and any questions answered, the subject must provide consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions. No research activities may be initiated until valid consent has been obtained from the subject.

10.3 Protocol Compliance/Amendments/Discontinuation

The study may be modified or discontinued at any time by the principal investigator, FDA, NIH, IRB/IEC, OHRP or other government agencies as part of their duties to ensure protection of research subjects. Deviations or changes to the protocol will be submitted for review and approval from all relevant oversight entities except where necessary to eliminate an immediate hazard to subjects (as necessary) or when the changes are only logistical or administrative aspects of the trial (e.g. change of telephone numbers). All such changes will be forwarded to the IRB/IEC at each site for approval.

10.4 Subject Confidentiality

Subject names will not appear on any research materials. If the subject name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor or study monitors. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the regulatory oversight agencies or representatives of the sponsor (e.g. study monitors). Only the Subject ID (a random unique code) will be recorded on relevant study documents (e.g. source worksheets).

Laboratory specimens will be coded. All samples will be used specifically for research purposes.

Computer entry and networking programs will be created using Subject ID. No identifying information will be stored in the study database. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be told that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records (source) to verify the information collected and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. Research charts with source documents will be kept double-locked and only available to study staff. The file linking subject IDs to specific patients will be stored on a password-protected computer only available to study staff.

10.5 RESEARCH INFORMATION IN MEDICAL RECORDS

Research data from this study including indication of study participation and lab test results will be included in subjects' medical records.

11.0 TRIAL MANAGEMENT

11.1 Coordination Efforts

Project coordination, data management, and biostatistical services will be provided through the Department of Neurology and Department of Biostatistics and Computational Biology at the University of Rochester in collaboration with the Principal Investigator.

11.2 Quality Assurance

To ensure optimal treatment of subjects and conduct of the research study according to Good Clinical Practice guidelines, study activities will be monitored for accurate, timely study progress and data collection in an ongoing manner.

11.3 Data Handling & Record Keeping

The University of Rochester will also maintain regulatory documentation. The Investigator or Coordinator should have the following study documents accessible during the study:

- Protocol (and amendments, if applicable)
- Signed and dated IRB/IEC approval of protocol, consent forms and advertisement notices (if applicable), documentation of IRB/IEC composition, and all IRB/IEC correspondence
- IRB/IEC approved consent form (sample) and advertisement for recruitment (if applicable)
- Copies of completed source worksheets
- Confidentiality agreement
- Up to date signed CVs for all personnel listed on the Log of Investigators and Study Staff

- Copy of professional licensure/registration, as applicable, for each individual named on the Log of Investigators and Study Staff, who has direct subject contact
- Log of Investigators, Study Staff and Staff-Related Duties
- Human Subject Protection Training Certificate for each individual named on the Authorization Log who has direct subject contact (if applicable, Health Insurance Portability and Accountability Act (HIPAA) Certification)
- Signed and dated Indemnity/Insurance statement *(Note: this may be filed in a separate business office)*
- Laboratory reference ranges and accreditation
- Copies of laboratory reports/printouts
- Signed subject consent forms
- Study drug supply/receipt/shipping records
- All correspondence
- Subject Identification Logs
- Serious adverse event report forms

11.4 Retention of Study Records

The following records must be retained by the investigator for a *minimum* of 2 years after the sponsor has notified the FDA that investigations have been discontinued or after the FDA has approved the new drug application:

- Signed informed consent documents for all subjects
- Subject identification code list, screening projections log
- Record of all communications between the investigator and the IEC/IRB
- Composition of the IEC/IRB or other applicable statement
- Record of all communications between the investigator and Sponsor or CTCC
- Authorization Log (List of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant trial-related duties, together with their roles in the study and their signatures)
- Copies of study forms and of documentation of corrections for all subjects
- Drug accountability records
- Record of any samples retained
- All other source documents (subject records, hospital records, laboratory records, etc.)
- All other documents as listed in ICH Guideline E6 (Good Clinical Practice: Consolidated Guidance)

12.0 PUBLICATION OF RESEARCH FINDINGS

The investigator intends to publish trial results. No research findings presented at meetings or in publication form will contain subject identifying information.

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