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A randomised, placebo-controlled trial of dutasteride in spinal and bulbar muscular atrophy

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Summary

Background—Spinal and bulbar muscular atrophy (SBMA) is caused by polyglutamine expansion in the androgen receptor, which results in ligand-dependent toxicity. Animal models have a neuromuscular deficit that is mitigated by androgen-reducing treatment.

Methods—We explored the efficacy and safety of the 5-alpha-reductase inhibitor, dutasteride, in a single-site, two-year, double-blind, placebo-controlled clinical trial. Physical, neurophysiological, quality of life, and biochemical outcomes were assessed in 50 ambulatory, symptomatic, genetically confirmed, male SBMA subjects randomised to receive dutasteride or placebo (25 in each group).

Findings—At 24 months, the placebo group showed a decrease of 5% (−0.30 kg/kg) in the primary outcome measure, change in weight-scaled muscle strength as indicated by quantitative muscle assessment (QMA), and the dutasteride group showed an increase in strength of 1% (+0.14 kg/kg); the difference between the groups (6%; CI 18%, −6%) was not significant. Secondary

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Conflicts of interest
ADK owns stock in GlaxoSmithKline, Inc.. MJW's stipend was paid by a fellowship from the NIH Clinical Research Training Program, which is supported in part by funds paid to the NIH Foundation by Pfizer, Inc.. NADP is currently employed by and receives stock options from Johnson & Johnson. KHF serves as an unpaid member of advisory boards for Biogen Idec and Prosensa.

Author contributions
LEFR was involved in the study conduct and data collection. With the guidance of CJC and NADP, ADK was primarily responsible for conducting the study and collecting and preparing the clinical data. LEFR, MJW, SA, and KHF were involved in data interpretation and manuscript preparation. CAW helped with the manuscript preparation. SA and NOJ conducted the statistical analyses. JAS and EWL gathered the data for the primary outcome measure. TJL, LL, JER and BIS collected data for the secondary outcome measures. JAS and MOHL were involved in the interpretation of physical functioning outcome data. ALP and ABS facilitated confirmatory genetic testing and served as unblinded facilitators for the interim analysis. CJC, NADP, and KHF were involved in the study concept and design.

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measures of creatine kinase, muscle strength and function, motor and sensory nerve conduction, activities of daily living, and erectile function did not show a significant difference between the study groups in change from baseline. However, quality of life as measured by the SF-36v2 physical component summary favored dutasteride, while the mental component summary favored placebo. The dutasteride group had fewer falls; there were no other significant differences in reported adverse events.

Interpretation—This study did not show a significant effect of dutasteride on the progression of muscle weakness in SBMA, although there were secondary indications of benefit. A longer trial duration or larger number of subjects may be needed to show an effect on the disease progression. Performance testing, QMA, and quality of life measures were identified as potentially useful endpoints for future therapeutic trials.

Funding—National Institutes of Health

Keywords

Kennedy's disease; spinal and bulbar muscular atrophy; motor neuron disease; androgen; dutasteride

Introduction

Spinal and bulbar muscular atrophy (SBMA, Kennedy's disease) is an uncommon neurodegenerative disease characterized by muscle weakness.1 The disease is progressively disabling and may be fatal. There is currently no effective treatment. In addition to bulbar and extremity muscle weakness, SBMA patients may have manifestations of androgen insensitivity.2 The cause of SBMA is a repeat expansion in the androgen receptor (AR) gene that causes a toxic gain of function in the AR protein and leads to a loss of spinal and bulbar motor neurons.3

The toxicity of the mutant AR in SBMA depends on androgens. This ligand dependence is indicated by prevention of the SBMA phenotype with castration in male transgenic mice and the induction of the phenotype in female mice with androgen administration.[4] These findings led to recent randomised clinical trials of leuprorelin, which reduces androgen levels. At 48 weeks, leuprorelin was associated with significantly improved swallowing function in a phase 2 study[5] but not in a subsequent phase 3 trial.[6]

Inhibitors of 5-alpha-reductase have not been tested previously in SBMA. These agents block the conversion of the androgen testosterone to dihydrotestosterone (DHT)[7] and offer the opportunity to decrease the toxic effects of DHT while sparing the anabolic effects of testosterone. Here we report a randomised, placebo-controlled trial of the 5-alpha-reductase inhibitor dutasteride in subjects with SBMA. An important aspect of this study was to evaluate outcome measures for future studies of the disease.

Methods

Subjects

This was a single-site study done at the National Institutes of Health (NIH) Clinical Center in Bethesda, MD, USA. Fifty-seven subjects with SBMA were recruited from May to November 2006 with the help of a patient organization, the Kennedy's Disease Association. Inclusion criteria were genetically confirmed SBMA with neurological symptoms, ability to walk 100 feet (30 m), willingness to participate in the trial design, and male sex. Exclusion criteria were age less than 18 years; female sex; a history of hypersensitivity to dutasteride or 5α-reductase inhibitors; exposure to 5α-reductase inhibitors, anti-androgens, testosterone,

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or steroids in the preceding 6 months; history of taking potent CYP3A4 inhibitors for over 4 weeks; any preexisting liver disease; alkaline phosphatase, gamma glutamyl transferase (GGT), or direct bilirubin greater than 1.5 times the upper limit of normal; serum transaminases greater than 1.5 times the upper limit of normal in subjects with normal creatine kinase levels; creatinine greater than 1.5 times the upper limit of normal; platelet count, white blood cell count or hemoglobin below the lower limit of normal; and other clinically significant medical disease that, in the judgment of the investigators, would expose the patient to undue risk of harm or prevent the patient from completing the study. Seven subjects were excluded due to elevated blood liver enzymes or hemoglobin levels below the lower limit of normal. The remaining 50 subjects did not meet the exclusion criteria and were enrolled in the study. The number of subjects for enrollment was chosen before the start of the study to detect a 50% decrease in the estimated 5% per year rate of decline in muscle strength. The rate of decline in muscle strength had not been previously determined for SBMA, and so the rate was estimated based on clinical experience. A power analysis indicated that 20 individuals would be needed for each arm to achieve 80% power for a two-sided t-test with 0.05 significance level threshold. To allow for dropouts, the target enrollment was 25 individuals per arm.

The National Institute of Neurological Disorders and Stroke (NINDS) Institutional Review Board and a data and safety monitoring board (DSMB) approved and oversaw this study, and all subjects gave written informed consent before enrollment. This trial was registered with ClinicalTrials.gov (NCT00303446).

Study design and conduct

A comprehensive report of the baseline data for this study has been published elsewhere.[8] Subjects received either 0.5 mg/day of dutasteride or placebo orally (figure 1) for 24 months between May 2006 and November 2008. There was no open-label extension. All subjects had physical, respiratory, and speech and swallow therapy evaluations at the NIH Clinical Center. There was no difference between the groups in the evaluations that were done, and no therapy was offered during the course of the study. Primary care physicians evaluated subjects between visits to the NIH, providing an assessment of general physical health every 3 months during the trial.

The subjects were randomised with a random number table in blocks of 4 or 6 subjects by the NIH Clinical Center Pharmacy, which dispensed the active agent or placebo according to subject enrollment number. The subjects were enrolled by ADK, who remained blind to the assignment and hormone levels, as were all who collected the data and did the final analysis. The DSMB was unblinded to the study agent assignments and evaluated an interim analysis. This was done after all subjects had completed 12 months of the study. The 12 month values for the primary outcome measure for the dutasteride and placebo groups were compared by t-test. The predetermined plan was to stop the study if the p-value was < 0.005 favoring dutasteride or < 0.05 favoring placebo. The analysis gave a p value of 0.49 and thus did not meet either of these criteria, and the study was continued until all subjects reached the 24 month endpoint.

Subjects reported the severity and type of adverse events at each visit. Subjects were given supplies of study drug at each visit, and compliance was based on residual pill counts.

Efficacy procedures

Quantitative muscle assessment (QMA) was the primary outcome measure. Additional outcome measures included a bulbar strength scale and manual muscle testing, performance testing and 2 minute timed walk, self-assessed quality of life, electromyography and nerve

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conduction studies, and biochemical profiles. Primary and secondary efficacy outcome measures were evaluated at the initial, 12-, and 24-month visits. After the study started, barium swallow and pulmonary function studies were added (see below).

Strength and physical function

QMA was done with a fixed frame dynamometer, a strain gauge tensiometer, and a computer-aided acquisition system (Aeverl Medical, Gainesville, GA). Maximal voluntary isometric muscle contractions were measured twice by two experienced examiners (EWL and JAS), and the average was calculated. Before starting the study, QMA procedures were practiced 8–10 hours for consistency between examiners, followed by separate examiner testing of 10 healthy age and gender matched controls. Intrarater and interrater reliability was high (ICCs = 0.93). The QMA was standardized by testing the subjects at the same time of day and with the same order of muscle group testing, by setting the joint angles with a goniometer, and by zeroing the load cells before each muscle group test. The bulbar rating scale (BRS) includes eight domains each rated on a 1–4 scale, abnormal to normal (supplemental table 1). Previous bulbar assessments were used to tailor the BRS to SBMA.[9] The original 8–32 point scale was transformed to percent maximum score (0–100%).

Three experienced examiners (NADP, CJC, ADK) performed manual muscle testing using a modified Medical Research Council scale (supplemental table 2); the average muscle score was based on 22 muscle groups.

Muscle performance was measured with the Adult Myopathy Assessment Tool (AMAT), which includes 7 timed functional tasks and 6 endurance tasks (supplemental table 3), with high interrater and intrarater reliability (ICCs = 0.95–0.98)[10] and correlation with other physical assessments such as QMA, gait speed, and the physical quality of life (Harris-Love *et al*., unpublished).

Timed walk tests have been used previously in SBMA.[11] In the current study, the subjects did a 2-minute walk in a 15 meter corridor three times, and the distance covered in the third of the three attempts was entered.[12] The subjects were allowed to use an assistive device and to rest up to 2 minutes between the trials.

Self-assessed quality of life

At each visit subjects rated their daily activity with a modified 9-question Activities of Daily Living (ADL) questionnaire (0–4, fully impaired to normal).[13]

Subjects completed the Medical Outcomes Study Short Form Version 2 (SF-36v2) by QualityMetric, Inc. (Lincoln, RI), in which they rated their quality of life over the preceding 4 weeks. Raw SF-36v2 scores were converted to norm-based scales and physical and mental component summaries using the scoring code provided by QualityMetric (SAS 9.1.3, SAS Institute, Cary, NC).

Sexual function was rated using the International Index of Erectile Function (IIEF). The total IIEF score (5–75) was reported as the percent maximum (0–100%).[14]

Neurophysiological studies

SBMA involves sensory as well as motor neurons.8 Nerve conduction studies were therefore done on four sensory nerves (median, ulnar, radial, sural) and two motor nerves (median, peroneal) using standard methodology and department-based normal values.15 Motor unit number estimation (MUNE) was done with a statistical MUNE program, a Nicolet Viking Select machine (Cardinal Health, Dublin, OH), and Shefner modification16 on the abductor

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pollicis brevis.17 All subjects were evaluated on the right side unless severe atrophy produced very low compound muscle action potentials (CMAPs), in which case the left side was used or the abductor digiti minimi was substituted.

Biochemical and hormonal profiles

Blood samples were drawn after overnight fast. Testing of hormonal levels is detailed in the legend to table 2. Biochemical panels and blood counts were performed by the NIH Clinical Center Chemistry Department.

Swallow function

After the start of this study, an effect on swallowing was reported in another study of leuprorelin in SBMA;[5] because of this, we opted to include swallowing evaluations in the current study. Subjects who presented at baseline with complaints of bulbar impairment received initial speech and swallow evaluations (n = 15). Modified barium swallow studies were done at 12 and 24 months on all subjects. Twenty-five domains were assessed, and six were chosen for final analysis based on the abnormal findings in subjects evaluated at baseline. All other domains were within normal range. Abnormal findings included vallecular pooling and repeated-swallow, each assessed with thin liquids, purees, and solids The domains were rated by the speech language pathologist using a Likert rating scale of 1–4 (1=normal: 2=mild difficulty; 3=moderate difficulty and 4=severe difficulty

Pulmonary function

After the study started, one subject developed serious respiratory difficulties (see below); because of this, the DSMB recommended that we include pulmonary function tests as an additional safety measure. Forced vital capacity (FVC) was measured by respiratory therapists at 12 and 24 months, and the percent of the reference value was calculated.[18]

Statistical methods

The final analysis of the primary outcome was adjusted for the interim analysis to limit the chance of falsely observing benefit at either 12 or 24 months to $p < 0.05$ overall.

Generalized estimating equation (GEE) models were used to examine the study agent's effect on the percent change from baseline in weight-scaled QMA total force as well as on the secondary outcomes. A covariance structure for multiple measurements of change per subject was modeled, in order to take into account repeated measures of the same subject. The first GEE model contained three predictors: time, treatment, and interaction between time and treatment. Using the first model, inferences were made whether or not rates of change were different between placebo and dutasteride groups. Second, if there was no significant interaction between time and treatment, the second GEE model containing time and treatment only was used to test whether there was a consistent difference between treatment groups. If there was significant interaction between time and treatment, then a two sample t-test with Satterthwaite approximation (if necessary) was used at each time point.[19]

Descriptive statistics such as mean, standard deviation (SD), and standard error (SE) were calculated to characterize the outcome measures. Chi-squared tests were used to compare the number of placebo and dutasteride subjects reporting adverse events (AEs) in Table 5. Paired t-tests were used to compare time points within the placebo group for Table 6. All p-values reported are two-sided. All statistical analyses, especially PROC GENMOD for GEE models, were performed using SAS software (v 9.1.3, SAS Institute, Cary, NC).

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Results

Demographics

The demographics of the 50 subjects randomised to placebo and dutasteride are summarized in table 1. The treatment groups were balanced with regard to age, CAG repeat length, disease duration, and body mass index. Six subjects did not complete the study (figure 1); the remaining 44 subjects were compliant at 24 months and were included in the final analysis.

Compliance and biological effect

At 12 months the placebo group took 1 ± 3 additional capsules and dutasteride missed 3 ± 3 capsules per 100 (p=0.04). At the 24-month visit the placebo and dutasteride groups missed 1 ± 3 and 3 ± 4 pills, respectively; this was not a significant difference.

Testosterone levels were unchanged with dutasteride administration (table 2). DHT levels decreased significantly in the dutasteride treated group compared to placebo ($p<0.0001$, table 2), as expected.

Primary measure of efficacy

From baseline to 24 months there was a 4.5% average decrease in weight-adjusted total QMA in the placebo group and a 1.3% increase in the dutasteride group (table 3). Due to variability in the outcome, the change from baseline was not significantly different between the two groups (figure 2). Post-hoc analysis showed no difference between the groups when the subjects were separated as greater or lesser than the median in duration of weakness, age, repeat length, or baseline QMA (supplemental table 4).

Secondary measures of efficacy

Similarly, creatine kinase; manual muscle testing; AMAT; timed 2-minute walk; BRS; median, ulnar, radial, and sural sensory nerve action potentials (SNAPs) and the SNAP average; median and peroneal CMAPs; MUNE; ADL; IIEF; and FVC did not show a significant difference between the study groups in change from baseline (table 4, supplemental table 7).

A subset of 15 subjects underwent initial barium swallow studies. These subjects showed no significant difference between cohorts in their swallow score, an average of six domains.

The SF-36v2 Physical Component Summary (PCS) favored dutasteride over placebo at 24 months as percent change from baseline (p=0.004; supplemental figure 1A) and in absolute change from baseline (p=0.01; table 4). There was a 6-point difference at 24 months, with the placebo group declining 4 points and the dutasteride group increasing 2 points from baseline. Conversely, the Mental Component Summary (MCS) favored placebo over dutasteride at 24 months (p=0.03; supplemental figure 1B). The placebo group increased 3 points in MCS score, and the dutasteride group declined 3 points (table 4).

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Adverse events

The only AE type to show a difference between the groups was falls, where the dutasteride group reported fewer events (p=0.048; table 5).

Nine AEs were categorized as serious (supplemental table 5). In the placebo group, two subjects were hospitalized after falls. In the dutasteride group, one subject died with autopsy-confirmed hypertensive and arteriosclerotic cardiovascular disease, and another subject developed serious respiratory difficulties and discontinued the study agent (figure 1). Biochemical profiles showed only minor differences between the groups (supplemental table 7). There was a relative increase in GGT in the dutasteride group compared to placebo, although the mean value after 24 months (33 ± 21) was still less than the mean reported in age-matched healthy controls (40 ± 3).[20] No differences between the dutasteride and placebo groups were seen with other liver function tests.

Rate of disease progression

To assess the usefulness of the various outcome measures in characterizing disease progression, we did a posthoc analysis of those measures that showed a decline from baseline to 24 months in the 23 placebo subjects (table 6). The SF-36v2 PCS showed the largest rate of decline at 5.2% per year, followed by the AMAT, which declined at 4.5% per year. Only the AMAT showed a significant decline from baseline at 24 months (p=0.004).

The z-score (mean change/SD) is an indication of the power of a given outcome measure to detect disease progression and can be used to guide the selection of endpoints in future trials. The AMAT score showed less variability than the other measures, and had the best z-score, followed by the SF-36v2 PCS, weight-scaled QMA, and median CMAP (table 6).

The relatively slow rate of decline in the QMA is such that a study would have to run much longer to detect a 50% benefit in a randomised clinical trial. In contrast, the AMAT and SF-36v2 PCS would require a shorter study period to detect a beneficial effect on disease progression.

The barium swallow studies done in a subset of 5 placebo subjects at baseline showed a 7.2% per year decline in the average score from baseline to 24 months (table 4). Similarly, a 6.1% decline was seen among the 21 placebo subjects followed from 12 to 24 months only (data not shown).

Discussion

Several recent findings implicating androgens in SBMA provided the rationale for this study: (1) DHT caused neurodegeneration in a fly model of SBMA;21 (2) male transgenic mice develop progressive weakness, and females are relatively unaffected; motor function improved in the males with androgen reduction, and the females developed weakness with androgen administration;4›22 (3) two sisters homozygous for the AR repeat expansion had only mild manifestations, indicating that SBMA in humans as in mice is male-limited, presumably because of higher androgen levels in males.23 Together, these observations provided impetus for testing androgen-reducing therapy in SBMA.

The drug leuprorelin has shown benefit in mouse models of SBMA, and more recently some indications of efficacy in human subjects.[5] Leuprorelin decreases testicular testosterone production. Dutasteride offers a more selective approach to decreasing androgens. Differential expression of 5-alpha-reductase in skeletal muscle and motor neurons suggests that DHT may be the primary ligand for the AR in motor neurons, while testosterone serves this role in skeletal muscle.[24,25] Thus, suppression of DHT production may decrease the

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toxic activation of the mutant AR in motor neurons without disrupting the beneficial anabolic action of testosterone in muscle.

In this study 50 men with SBMA were randomised to receive placebo or dutasteride for 24 months. DHT levels decreased markedly in the dutasteride group, indicating an appropriate pharmacological effect. QMA, an outcome measure previously used in amyotrophic lateral sclerosis and muscular dystrophy studies,[26] did not show a significant difference at 12 or 24 months between the study groups. There was no open-label extension, such as might have given an indication of a longer term effect, albeit uncontrolled. In retrospect this study was under-powered. Given the slow progression of weakness in the placebo group, more time or a larger number of patients may be needed to show a decrease in the rate of progression using QMA. Of the secondary measures, AMAT and SF-36v2 PCS may be better for use in future trials.

Analysis of the SF-36v2 PCS and MCS revealed positive and negative effects. Subjects receiving dutasteride had an increase in PCS scores at 24 months, while PCS scores for the placebo arm decreased. In contrast, MCS scores for the dutasteride study arm at 24 months showed a decrease from baseline, while placebo MCS scores increased. Other self-assessed parameters, including ADL and IIEF, did not show a significant difference.

Dysphagia is an important source of morbidity in SBMA. The six barium swallow parameters reported here represent the common areas of difficulty in this population. The average swallow score did not show a significant difference at 12 or 24 months. However, is not possible to draw a clear conclusion from this subset due to selection bias. In the phase 2 leuprorelin trial, Banno *et al.* reported increased cricopharyngeal opening time with leuprorelin.[5] However, a later phase 3 study did not confirm a significant effect on swallow function.[6]

Dutasteride was generally well tolerated in our population, with a low dropout rate and high compliance. There was a difference in the number of subjects reporting musculoskeletal AEs, with fewer dutasteride subjects reporting events in this category. Most of this difference is attributable to falls, which like the SF-36v2 PCS might indicate a benefit of dutasteride that was not detected as significant with QMA and the other secondary measures. In other studies, dutasteride's most common adverse effects included impotence and decreased libido;[27] these may have contributed to lower MCS scores in the dutasteride group.

The data collected from this trial provides an indication of the rate of decline for various measures over 24 months in a placebo group. The SF-36v2 PCS, AMAT, and swallow scores showed the greatest percent decline per year. This data can be used in future trials of other agents, such as HSP90 inhibitors,[28] ASC-J9,[29] and IGF-1,[30] which have been shown to improve motor function in mouse models.

The finding that dutasteride had no significant effect on muscle strength as measured by QMA after 24 months likely reflects the complex role of androgens in SBMA as well as the sensitivity of the test. Whereas androgens contribute to the toxicity of the mutant AR in mouse models of SBMA, higher blood androgen levels correlated with increased muscle strength in a cross-sectional study of this patient population.[8] Based on these results, we do not currently recommend dutasteride as treatment for SBMA. Nevertheless, there are indications of potential benefit that point to the need for further investigation of androgen-lowering therapy. The current study contributes to our understanding of SBMA and indicates that future clinical trials need to take into account the rate of decline and use clinically meaningful outcome measures that can reliably predict a therapeutic benefit.

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Supplementary Material

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Abbreviations

ADL	Activities of Daily Living
AE	adverse event
AMAT	Adult Myopathy Assessment Tool
BRS	Bulbar Rating Scale
CMAP	compound muscle action potential
DHT	dihydrotestosterone
DSMB	Data and Safety Monitoring Board
FT	free testosterone
GGT	gamma glutamyl transferase
IIEF	International Index of Erectile Function
MCS	mental component summary of the SF-36v2
MUNE	motor unit nerve estimation
NIH	the National Institutes of Health

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NINDS	National Institute of Neurological Disorders and Stroke
PCS	physical component summary of the SF-36v2
QMA	Quantitative Muscle Assessment
SBMA	spinal and bulbar muscular atrophy
SD	standard deviation
SE	standard error
SF-36v2	Medical Outcomes Study 36-item Short Form Version 2
SNAP	sensory nerve action potential
TT	total testosterone

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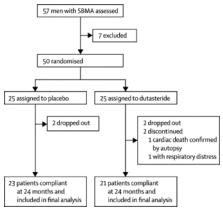

Figure 1. Study profile

Four subjects dropped out of the study in the first 6 months due to travel difficulties in coming to the NIH from elsewhere in the United States and Canada. One subject died between his 3 and 6 month visits; an autopsy was consistent with a cardiac cause of death. One subject developed respiratory distress and declined rapidly during his 6 months of enrollment. He was removed from the study and hospitalized until his vital capacity and symptoms stabilized. No other cause for his respiratory failure was identified. He subsequently continued to decline and died about one year later. Thus, while the safety analysis was done on 25 subjects in each group, the efficacy analysis at 24 months was done on 23 subjects in the placebo group and 21 subjects in the dutasteride group.

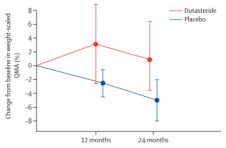

Figure 2. Percent change from baseline in QMA, the primary outcome measure

The difference between placebo (blue) and dutasteride (red) was not significant. Bars indicate standard error of the mean.

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Table 1

Subject demographics

The data represent 25 subjects in each study group at baseline.

	Placebo Mean ± SD (range)	Dutasteride Mean ± SD (range)
Age (years)	53.5 ± 9.2 (39–71)	51.9 ± 10.5 (37–79)
CAG repeat length (n)	46.5 ± 2.0 (44–51)	47.1 ± 2.8 (43–53)
Duration of weakness (years)	11.4 ± 7.0 (0–28.1)	12.0 ± 9.4 (1.0–42.2)
Body mass index (kg/m^2)	27.8 ± 4.1 (22.5–40.6)	28.1 ± 5.8 (17.3–40.2)

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Table 2

Hormonal profile of subjects during the study

Baseline total and free testosterone testing was done at Mayo Medical Laboratories (Rochester, MN) by HPLC/tandem mass spectrometry and equilibrium dialysis (reference ranges of 240–950 ng/dl and 9–30 ng/dl, respectively). The 12 and 24 month assays were done at the NIH Clinical Center Chemistry Department (Bethesda, MD) with a chemiluminescence immunoassay for total testosterone (reference ranges: 262–1593 ng/dl for ages 20–49 years and 181–758 ng/dl for >49 years) and free testosterone calculated based on the total testosterone and albumin levels (reference range = 7.5–22.6 ng/dl). Dihydrotestosterone (DHT) levels were measured by Esoterix, Inc. (Calabasas Hills, CA). The p-values given for total and free testosterone compare the placebo and dutasteride groups over the course of the study (baseline to 12 and 24 months) based on GEE models; the p-values for dihydrotestosterone are for comparison of the groups at 12 and 24 months by t-test (see Methods).

		Placebo Mean ± SD	n	Dutasteride Mean ± SD	n	p-value*
Total testosterone (ng/dL)	Baseline	627 ± 181	25	625 ± 329	25	
	12 Mo.	497 ± 226	23	602 ± 299	21	
	24 Mo.	542 ± 192	23	566 ± 241	21	0.77
Free testosterone (ng/dL)	Baseline	14.5 ± 4.8	25	13.2 ± 5.2	25	
	12 Mo.	10.5 ± 3.7	23	11.5 ± 6.2	21	
	24 Mo.	10.0 ± 3.0	23	9.8 ± 4.1	21	0.68
Dihydrotestosterone (ng/dL)	Baseline	44.6 ± 18.4	25	45.7 ± 31.6	25	
	12 Mo.	44.2 ± 23.3	23	5.3 ± 2.3	21	**<0.0001**
	24 Mo.	41.8 ± 19.1	23	5.3 ± 3.2	21	**<0.0001**

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Table 3

Primary outcome measure

Data represent the placebo and dutasteride study arms at baseline (n = 25, 25), 12 (n = 22, 21), and 24 months (n = 23, 21). The p-values compare the placebo and dutasteride groups over the course of the study based on GEE models (see Methods). One subject in the placebo group was not evaluated at 12 months due to pain from a recent fall. Specific muscle groups and composites can be found in supplemental table 6.

		Placebo Mean ± SD	n	Dutasteride Mean ± SD	n	Difference between Dutasteride and Placebo (95% CI)	p-value
Quantitative Muscle Assessment							
Weight scaled total force (kg/kg)	Baseline	4.06 ± 1.39	25	3.42 ± 1.77	25		
	12 Mo.	3.90 ± 1.26	22	3.60 ± 1.80	21		
	24 Mo.	3.76 ± 1.31	23	3.56 ± 1.75	21		0.19
Percent change in weight scaled	12 Mo.	−2.2 ± 9.4	22	3.1 ± 27.1	21	5.2 (17.4, −7.1)	
Total force	24 Mo.	−4.5 ± 13.5	23	1.3 ± 24.2	21	5.8 (17.6, −5.9)	0.28

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Table 4

Secondary outcome measures

Additional biochemical test and sub-scores for secondary outcomes can be found in supplemental table 7. The p-values compare the placebo and dutasteride groups over the course of the study based on GEE models (see Methods).

	Placebo Mean ± SD				Dutasteride Mean ± SD				Difference in Change at 24 months (95% CI)	p-value
	Baseline	Change at 24 months (%)[a]		n[b]	Baseline	Change at 24 months (%)[a]		n[b]		
Creatine kinase (U/L)	1181 ± 761	−19 ± 494	(−1.6)	25, 23	1041 ± 781	−62 ± 472	(−6.0)	25, 21	−43 (251, −338)	0.86
Manual muscle testing average	9.10 ± 0.75	0.02 ± 0.74	(+0.2)	25, 23	8.68 ± 1.04	0.01 ± 0.51	(+0.1)	25, 21	−0.01 (0.39, −0.39)	0.47
Adult Myopathy Assessment Tool total	31.2 ± 8.8	−2.8 ± 4.2	(−9.1)	25, 23	27.0 ± 11.5	−1.5 ± 3.9	(−5.6)	25, 21	1.3 (3.8, −1.2)	0.13
Timed 2-minute walk (m)	85.4 ± 37.0	15.2 ± 30.7	(+17.8)	25, 23	77.6 ± 38.8	26.9 ± 35.9	(+34.6)	25, 20	11.71 (32.23, −8.81)	0.28
Swallow score average	3.67 ± 0.35	−0.53 ± 0.46	(−14.5)	6, 5	3.69 ± 0.37	−0.14 ± 0.54	(−3.8)	9, 7	0.39 (1.06, −0.28)	0.11
Bulbar rating scale (%)	89.8 ± 6.5	6.4 ± 5.8	(+7.1)	25, 23	91.2 ± 7.0	3.9 ± 4.6	(+4.2)	25, 21	−2.5 (0.7, −5.7)	0.08
Sensory nerve action potential average (μV)	4 ± 3	0 ± 1	(0.0)	25, 23	4 ± 2	0 ± 1	(0.0)	25, 21	0 (0.5, −0.7)	0.73
Median compound muscle action potential (mV)	7.23 ± 2.37	−0.23 ± 1.84	(−4.1)	25, 22	5.28 ± 3.52	0.24 ± 1.89	(+4.6)	25, 21	0.48 (1.63, −0.67)	0.37
Peroneal compound muscle action potential (mV)	3.18 ± 1.72	0.15 ± 1.37	(+6.8)	25, 22	2.44 ± 2.32	0.04 ± 0.81	(+1.6)	25, 21	−0.11 (0.59, −0.80)	0.65
Motor unit number estimation (n)	48.4 ± 20.8	−2.2 ± 23.3	(−4.4)	25, 23	40.0 ± 24.1	−2.6 ± 17.5	(−7.0)	25, 19	−0.4 (12.8, −13.5)	0.99
Activities of daily living total	26.3 ± 4.1	1.2 ± 3.3	(+4.4)	24, 22	25.5 ± 6.1	1.1 ± 4.2	(+4.4)	25, 21	−0.1 (2.3, −2.3)	1.00
Physical component summary (%)	35.2 ± 9.9	−3.6 ± 8.4	(−10.3)	24, 22	34.0 ± 12.8	2.1 ± 6.1	(+6.3)	24, 21	5.7 (10.3, 1.2)	**0.01**
Mental component summary (%)	50.9 ± 12.7	3.3 ± 9.3	(+6.5)	24, 22	52.4 ± 11.1	−3.2 ± 10.2	(−6.2)	24, 21	−6.5 (−0.5, −12.6)	**0.03**
International Index for Erectile Function (%)	47.6 ± 38.3	−0.3 ± 16.4	(−9.5)	24, 20	43.9 ± 37.8	−3.5 ± 6.9	(−11.4)	25, 21	−3.2 (4.6, −11.1)	0.61

[a]The change at 24 months represents the average change from baseline within the study arm. Percent change from baseline was calculated for each study group (mean change from baseline/mean baseline group value × 100%).

[b]The numbers (n) represent the subjects in each study arm assessed at baseline and 24 months, respectively.

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Table 5

Distribution of adverse events

Shown are the adverse events reported by more than 10% or subjects (i.e., 3 or more) in either group. Listed are the number of subjects reporting the adverse events, with the number of events reported in parentheses. The p-values compare the number of adverse events reported by placebo and dutasteride subjects, based on chi-squared analysis.

	Placebo (n=25)	Dutasteride (n=25)	p-value
Adverse Events			
Bone fractures	4 (5)	3 (3)	0.684
Diarrhea	0	3 (9)	0.074
Dyspepsia	1 (1)	3 (5)	0.297
Falls	16 (63)	9 (40)	**0.048**
Fatigue	1 (2)	4 (11)	0.157
Gastrointestinal	6 (8)	4 (6)	0.480
Headache	9 (27)	11 (35)	0.564
Muscle cramps	5 (12)	5 (10)	1.000
Muscle weakness	4 (6)	2 (3)	0.384
Myalgia	5 (21)	4 (17)	0.713
Numbness	4 (5)	6 (8)	0.480
Other infections	4 (6)	1 (1)	0.157
Pain	10 (33)	9 (23)	0.771
Shortness of breath	0	3 (3)	0.074
Upper respiratory infections	12 (33)	14 (32)	0.571

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Table 6

Outcome measures showing a decline in the placebo group at 24 months

	Rate of decline[a] (%/year)	Paired *t*-test[b] p-value	Z-score[c] (mean change /SD)
AMAT total	4.5	0.004	0.68
SF-36v2 PCS	5.2	0.054	0.43
QMA weight scaled	2.3	0.116	0.34
Median CMAP	1.6	0.553	0.13
MUNE	2.3	0.654	0.09
IIEF	0.3	0.946	0.02

[a] Calculated as the mean change per year divided by the mean baseline value for the placebo group

[b] A paired t-test was used to assess the significance of the change from baseline to 24 months

[c] Calculated as the absolute value of the mean change from baseline divided by the SD of the change