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

Design: Open-label dose-escalation clinical trial.

Setting: University medical center.

Participants: Fifteen moderately affected ambulatory participants with genetically proven myotonic dystrophy type 1.

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

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

Results: All participants tolerated rhIGF-1/rhIGFBP-3. There were no significant changes in muscle strength or functional outcomes measures. Lean body muscle mass measured by dual-energy x-ray absorptiometry increased by 1.95 kg (P < .001) after treatment. Participants also experienced a mean reduction in triglyceride levels of 47 mg/dL (P = .002), a mean increase in HDL levels of 5.0 mg/dL (P = .03), a mean reduction in hemoglobin A1c levels of 0.15% (P = .03), and a mean increase in testosterone level (in men) of 203 ng/dL (P = .002) while taking rhIGF-1/rhIGFBP-3. Mild reactions at the injection site occurred (9 participants), as did mild transient hypoglycemia (3), lightheadedness (2), and transient papilledema (1).

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

Trial Registration: clinicaltrials.gov Identifier: NCT00233519

small clinical study of 9 patients with DM1, 4 months of receiving twice-daily, subcutaneous recombinant human IGF-1 (rhIGF-1) resulted in improved insulin action, increased muscle protein synthesis, decreased body fat, and increased plasma testosterone levels.5

Compared with rhIGF-1 alone, the circulating half-life of rhIGF-1 complexed with IGF binding protein 3 (rhIGF-1/rhIGFBP-3) following subcutaneous injection is extended, and adverse effects related to peak activity, mainly hypoglycemia, may be reduced.6 Treatment with rhIGF-1/rhIGFBP-3 is currently approved for children with severe primary IGF-1 deficiency and has been studied as a therapeutic agent for hip fractures, diabetes, and severe burns.7-10 This 2-component preparation of recombinant proteins may offer advantages for increasing the effects of rhIGF-1 on muscle while reducing peak-dose adverse effects. Its use in patients with DM1 has not yet been described.

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

METHODS

PARTICIPANTS

We performed a single-center, uncontrolled, dosage-escalation study of rhIGF-1/rhIGFBP-3 in 15 patients with DM1. The study was approved by the University of Rochester institutional review board (investigational new drug No. 68 861). All study participants provided written informed consent. Participants were aged between 21 and 60 years, had genetically confirmed DM1, could walk 30 feet without assistance (cane and leg bracing permitted), had significant distal weakness with some preservation of proximal strength, and met all prespecified inclusion/exclusion criteria (http://clinicaltrials.gov/ct2/show/study/NCT00233519).

TREATMENT AND FOLLOW-UP

The rhIGF-1/rhIGFBP-3 (Iplex, mecamserin rinfabate) was provided by INSmed Inc (Richmond, Virginia). Six patients were treated with 0.5 mg/kg/d of rhIGF-1/rhIGFBP-3 for 8 weeks followed by 1.0 mg/kg/d for 16 weeks (cohort 1). After review of the safety data by the data and safety monitoring board, dosage escalation was approved in the subsequent 9 participants, who received 0.5 mg/kg/d for 8 weeks, 1.0 mg/kg/d for 8 weeks, and 2.0 mg/kg/d for 8 weeks (cohort 2). After withdrawal of study medication at week 24, all participants were followed up for an additional 16 weeks.

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

OUTCOME MEASURES

The primary outcome measure was the ability of participants to complete 24 weeks of rhIGF-1/rhIGFBP-3 treatment. All other outcomes were considered secondary, with no prespecified priority. Each participant had 6 inpatient evaluations at the University of Rochester General Clinical Research Center (weeks 0, 8, 16, 24, 28, and 40) and 9 outpatient evaluations (weeks 2, 4, 6, 10, 12, 14, 18, 20, and 22). Serial safety monitoring included physical examinations, neuro-ophthalmic evaluations, blood cell counts, serum chemistry, coagulation times, lipid profiles, urinalysis, electrocardiography (ECG), and levels of thyroxine, thyroid stimulating hormone, γ-glutamyltransferase, hemoglobin A1c, estradiol (women), testosterone (men), C- peptide, and insulin. Ultrasounds of the abdomen and pelvis, chest and neck x-rays, and ECGs were used to monitor for organomegaly or adenopathy. Serial glucose testing (4 times per day) was obtained using a finger-stick glucometer for 10 days following all increases in medication. Fasting glucose levels were obtained every 2 weeks throughout the study. Serial free and total IGF-1 levels were drawn in the morning before rhIGF-1/rhIGFBP-3 injections. Total IGF-1 was measured at Esoterix Laboratories (Calabasas Hills, California), while analysis of free IGF-1 was performed at INSmed Therapeutic Proteins using the commercially available enzyme-linked immunosorbent assay kits from Diagnostic Systems Laboratory (Diagnostic Systems Laboratory, Webster, Texas).

Strength was evaluated by quantitative muscle assessment using a fixed dynamometer system on 12 muscle groups (6 on each side for the following: elbow flexion and extension, knee flexion and extension, shoulder abduction, and ankle dorsiflexion).13 Manual muscle testing was performed bilaterally using a modified Medical Research Council scale in a total of 26 muscle groups (shoulder abduction, elbow flexion/extension, wrist flexion/extension, hip flexion/extension/abduction, knee flexion/extension, ankle dorsiflexion/plantarflexion, and neck extension/flexion) as described by Personius et al.14 Other evaluations of muscle function included hand grip strength testing, myotonia testing,15-16 Purdue pegboard test17,18 a 6-minute walk test,19 forced vital capacity, and timed functional tests (time to traverse 30 feet, time to ascend 4 stairs, time to descend 4 stairs, and time to get up from a chair).20 Examinations were performed by 2 primary evaluators who documented interrater reliability every 6 months. Quality of life was measured with the Sickness Impact Profile.

Changes in skeletal muscle were evaluated using dual-energy x-ray absorptiometry, which has been established as a valid method for measuring lean body mass and has been shown to correlate well with muscle mass calculations obtained via total-body potassium 40 counting.21-22 Cognitive and gastrointestinal testing was implemented for the final 8 participants in response to early participant reports of improved clarity of thought and reduction of diarreal frequency while receiving treatment. This testing included the letter-number sequencing and vocabulary subtests from the Wechsler Adult Intelligence Scale III, the National Adult Reading Test, the Selective Reminding Test, the Rey Complex Figure Test, the Stroop Color Word Test, the Beck Depression Inventory (to monitor changes in mood), the Gastrointestinal Symptom Rating Scale modified for patients with irritable bowel syndrome (GSRS-IBS),23 and the Irritable Bowel Syndrome Impact Scale (IBS-IS).24

The schedule for the above evaluations is provided in eTable 1.

STATISTICAL ANALYSIS

All statistical tests were 2-tailed and were performed using a 5% significance level. Changes from baseline to each visit in laboratory test results, lean body mass, muscle function, quality of life, and cognitive test results were analyzed using a repeated measures analysis of covariance model that included the visit week (categorical) and baseline value of the outcome variable as independent variables. Ninety-five percent confidence intervals (CI) for mean changes were constructed using this model. Changes from baseline to week 24 were of primary interest. Similar analyses were performed for changes from week 24 (the last visit receiving treatment) to week 40 to evaluate the effects of drug withdrawal.
SAFETY AND TOLERABILITY

All 15 patients successfully completed the 40-week study. Eighty-nine of the 90 inpatient appointments were kept by participants. The most commonly reported adverse event was redness or pain at the injection site (9 participants). Transient lightheadedness occurred in 2 participants. One participant developed mild nontender enlargement of his left breast during the final 5 weeks of receiving 1.0 mg/kg/d of rhIGF-1/rhIGFBP-3 therapy. As gynecomastia can occur in DM1, the relationship to rhIGF-1/rhIGFBP-3 was uncertain. After completing the trial, the participant received testosterone supplementation therapy and his gynecomastia largely resolved.

Three adverse effects were considered moderately severe, all occurring in cohort 2. One participant, known to have gallstones prior to entering the study, had a cholecystectomy approximately 2 1/2 months into the washout period (week 33).

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

One participant showed mild papilledema on the last day of rhIGF-1/rhIGFBP-3 treatment at the 2.0 mg/kg/d dosage. This finding had not been present at week 8 or week 16. Concurrent medications included metronidazole, rifaximin, and Align probiotic. She had no headache or visual symptoms, and visual field testing was normal. Magnetic resonance images of the head and spinal fluid analysis appeared normal. A fundoscopic examination 4 weeks after discontinuation of the study medication and the above-mentioned drugs showed reduced optic nerve swelling. A fundoscopic examination 16 weeks after she stopped receiving medication was normal.

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

TOTAL AND FREE IGF-1 CONCENTRATIONS

As previously observed in DM1, mean basal levels of total IGF-1 in our study participants were in the lower reference range. Treatment with rhIGF-1/rhIGFBP3 resulted in a greater than 3-fold elevation of total IGF-1 levels (Figure 1). Mean levels of total IGF-1 remained elevated throughout the dose escalation period. The mean
concentration of free IGF-1 increased approximately 2-fold above baseline but remained in the reference range throughout the 24 weeks of therapy (Figure 2). Notably, similar levels of serum IGF-1 were observed in both cohorts at the completion of 24 weeks of treatment.

Figure 2. Mean free insulin-like growth factor 1 (IGF-1) levels. The reference range (0.65-5.20 ng/mL) is indicated by dashed lines (to convert to nanomoles per liter, multiply by 0.0259; testosterone to nanomoles per liter, 0.0347; triglycerides to millimoles per liter, 0.0113).

Table 2. Mean Changes in Measures of Muscle Mass and Strength, Functional Testing and Quality-of-Life, Laboratory Testing, and Gastrointestinal Survey Scores for Entire Sample

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

SKELETAL MUSCLE MASS

Lean body mass increased after the 0.5 mg/kg/d 8-week treatment interval (mean increase, 0.8 kg; 95% CI, 0.3-1.3; P = .003), with further increases reaching 1.95 kg (95% CI, 1.00-2.90; P < .001) at the completion of 24 weeks of treatment (Table 2, Figure 3). The mean increase in lean body mass after 24 weeks was slightly larger in cohort 2 than in cohort 1 (2.27 kg vs 1.36 kg). During the washout period, the lean body mass of both cohorts decreased (Figure 3).

LABORATORY TEST RESULTS

Changes in several laboratory values were observed after 24 weeks of rhIGF-1/rhIGFBP-3 treatment (Table 2; Figure 4). Triglyceride levels fell an average of 47.4 mg/dL.
### Variable

#### Treatment (Baseline-Week 24)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline, Mean (SD)</th>
<th>Mean Change (95% CI)</th>
<th>P Value</th>
<th>No.</th>
<th>P Value</th>
<th>Mean Change (95% CI)</th>
<th>P Value</th>
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<tr>
<td>DEXA lean body mass, kg</td>
<td>43.75 (9.32)</td>
<td>1.36 (-0.50 to 3.23)</td>
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<td>.03</td>
<td>-0.22 (-1.36 to 0.92)</td>
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<tr>
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<td>GMA score, %</td>
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<td>.88</td>
<td>-5.28 (-10.79 to 0.23)</td>
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<tr>
<td>BMI</td>
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<td>.01</td>
<td>-0.21 (-0.68 to 0.26)</td>
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#### Washout (Weeks 24-40)

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<th>Variable</th>
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<th>Mean Change (95% CI)</th>
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<tr>
<td>BMI</td>
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<td>.14</td>
<td>.01</td>
<td>-0.21 (-0.68 to 0.26)</td>
<td>.31</td>
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#### Entire Study (Baseline-Week 40)

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<th>Variable</th>
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<th>P Value</th>
<th>Mean Change (95% CI)</th>
<th>P Value</th>
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<td>MMT score</td>
<td>4.06 (0.35)</td>
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<td>.03</td>
<td>.88</td>
<td>-5.28 (-10.79 to 0.23)</td>
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<tr>
<td>BMI</td>
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<td>0.30 (-0.15 to 0.75)</td>
<td>.14</td>
<td>.01</td>
<td>-0.21 (-0.68 to 0.26)</td>
<td>.31</td>
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</tbody>
</table>

*See Table 2 for abbreviations, SI conversion factors, and footnotes; ellipses indicate data not available.*

### Table 4. Mean Changes in Measures of Muscle Mass and Strength, Functional Testing and Quality-of-Life, Laboratory Testing, and Gastrointestinal Survey Scores for Cohort 2 (n=9)

<table>
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<tr>
<th>Variable</th>
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<th>Mean Change (95% CI)</th>
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<th>No.</th>
<th>P Value</th>
<th>Mean Change (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
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<td>.03</td>
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<td></td>
</tr>
<tr>
<td>MMT score</td>
<td>4.11 (0.40)</td>
<td>0.10 (-0.21 to 0.41)</td>
<td>.49</td>
<td>.84</td>
<td>0.12 (-0.04 to 0.27)</td>
<td>.12</td>
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<tr>
<td>GMA score, %</td>
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<td>-0.74 (-6.20 to 4.77)</td>
<td>.77</td>
<td>80</td>
<td>-0.26 (-0.53 to 0.42)</td>
<td>.91</td>
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</tr>
<tr>
<td>BMI</td>
<td>22.65 (4.05)</td>
<td>0.96 (-0.04 to 1.93)</td>
<td>.06</td>
<td>21</td>
<td>0.34 (-0.46 to 1.17)</td>
<td>.37</td>
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</table>

*See Table 2 for abbreviations, SI conversion factors, and footnotes; the 6-minute walk testing was added after this cohort completed the study.*
moles per liter, multiply by 0.0347) during treatment. eTable 2 provides additional baseline and posttreatment laboratory test data.

GASTROINTESTINAL SURVEYS
AND COGNITIVE TESTING

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

There were no significant adverse changes in cognition while participants were receiving therapy. One of 7 cognitive tests showed a statistically significant improvement after 24 weeks (Rey Complex Figure Delayed Recall Score), with a mean improvement over baseline of 7.1 points ($P = .002$) during treatment and a decrease of 1.6 points ($P = .20$) during the washout period.

FIGURE 3. Mean changes in lean muscle mass measured using dual-energy x-ray absorptiometry for both cohorts; $n=15$ except for the week 24 visit ($n=14$). Error bars indicate the standard error of the mean; $* P<.05$ (compared with baseline).

This is the first study to use a 2-component preparation of recombinant proteins, rhIGF-1/rhIGFBP-3, for myotonic dystrophy. This study demonstrated that rhIGF-1/rhIGFBP-3 given for 24 weeks in escalating dosages is well tolerated in a cohort of patients with DM1.

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

FIGURE 4. Mean responses over time for testosterone, triglyceride, hemoglobin A1c (HbA1c), high-density lipoprotein (HDL) cholesterol, and fasting plasma glucose levels. Reference ranges are indicated by dashed lines. Error bars indicate the standard error of the mean.
Reduced or low reference levels of IGF-1 occur in patients with DM1 and may be corrected via therapeutics. The cause of reduced levels of IGF-1 in DM1 is not entirely clear but may relate in part to disturbances in the DM1 hypothalamo-pituitary-adrenal axis. Necrosis of muscle fibers, fibrosis of the muscle, and muscle contractures are less conspicuous in DM1 than in most other forms of dystrophy. Instead, both the synthesis and catabolism of muscle protein in these patients is slowed and the histopathology is characterized mainly by muscle fiber atrophy. The possibility that muscle weakness and atrophy are treatable in DM1 suggests that there may be a therapeutic role for conventional endocrine therapies. There is evidence that IGF-1 improves insulin resistance, promotes protein anabolism, and enhances cell growth. It is plausible that some of these effects may counter the anabolic deficiency in DM1 caused by insulin resistance, gonadal insufficiency, and decreased growth hormone.

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

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

This study had several limitations including small sample size and the absence of a placebo group. Results concerning the activity and efficacy measures must be interpreted with some caution owing to the large number of statistical tests performed. Particularly, for the evaluations of muscle strength and function, gastrointestinal symptoms, and cognition, practice and/or training effects or placebo effects (knowledge that the participants are receiving active treatment) could be responsible for some of the findings. Additional studies will be required to determine if the observed reductions in serum glucose, hemoglobin A1c, and triglyceride levels may ultimately have extended beneficial effects on a DM1 population predisposed to both impaired glucose tolerance and lipid abnormalities.

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

In summary, this is the first study to demonstrate the feasibility of using rhIGF-1/rhIGFBP-3 as a neuromuscular therapy for a muscular dystrophy. This is also one of the first evaluations of a 2-component preparation of recombinant proteins for any neurological disease. The results from this trial concerning the activity markers are encouraging but require longer controlled parallel group trials to clarify the longer-term efficacy, safety, and optimal dosage of rhIGF-1/rhIGFBP-3 as a treatment for DM1 and other muscular dystrophies.

Accepted for Publication: July 15, 2010.
Published Online: September 13, 2010. doi:10.1001/archneurol.2010.227
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Financial Disclosure: Dr Heatwole reports receiving grants from a National Institute of Arthritis and Musculoskeletal and Skin Diseases K23 award, a Muscular Dystrophy Association Translational Research Infrastructure grant, and a New York State Empire Clinical Research Investigator Program award. Dr Jackson reports receiving funding from INSMED Inc to perform a phase 2 trial of Iplex for myotonic dystrophy and from Cytokinetics to perform a phase 2 trial of amyotrophic lateral sclerosis and being on the advisory board for Avanair Pharmaceuticals. Dr McDermott reports receiving grants from the National Institutes of Health, Food and Drug Administration, Spinal Muscular Atrophy Foundation, Muscular Dystrophy Association, Michael J. Fox Foundation, and the National Institute of Child Health and Human Development, National Institute of Neurological Disorders and Stroke, National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute of Mental Health.
tion, Forest Research Institute, Medication Inc, Boehringer Ingelheim Pharmaceuticals Inc, and Neurosearch Sweden AB and being a consultant for the New York State Department of Health, American Epilepsy Society, Boehringer Ingelheim Pharmaceuticals Inc, and Teva Pharmaceuticals Ltd.

Funding/Support: This research was supported by the National Institute of Neurological Disorders and Stroke (award No. U54NS048843), the Muscular Dystrophy Association, the University of Rochester General Clinical Research Center and Clinical Translational Science Institute (funded by the National Center of Research Resources [UL1RR02160]), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (1K23AR053947), and the Saunders Family Neuromuscular Research Fund. The National Registry of Myotonic Dystrophy and FSHD Patients and Family Members (National Institute of Arthritis and Musculoskeletal and Skin Diseases [N01-AR-50-227450]) assisted with recruitment, and INSMED Inc provided the study medication for all participants.


Additional Contributions: The authors thank all of the participants of this study and their families for their commitment to medical research.

REFERENCES