Title

Safety, tolerability, and preliminary efficacy of an IGF-1 mimetic in patients with spinal and bulbar muscular atrophy: a randomised, placebo-controlled trial

Journal

The Lancet Neurology, 17(12)

ISSN

1474-4422

Authors

Grunseich, Christopher
Miller, Ram
Swan, Therese
et al.

Publication Date

2018-12-01

DOI

10.1016/s1474-4422(18)30320-x

Peer reviewed

HHS Public Access

Author manuscript

Lancet Neurol. Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

Lancet Neurol. 2018 December ; 17(12): 1043–1052. doi:10.1016/S1474-4422(18)30320-X.

A randomized, placebo-controlled study to evaluate the safety, tolerability, and preliminary efficacy of an IGF-1 mimetic in patients with spinal and bulbar muscular atrophy

Christopher Grunseich, MD,
Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD, USA

Ram Miller, MDCM,
Novartis Institutes for Biomedical Research, Cambridge, MA, USA

Therese Swan, PharmD,
Novartis Institutes for Biomedical Research, Cambridge, MA, USA

David J Glass, MD,
Novartis Institutes for Biomedical Research, Cambridge, MA, USA

Mohamed El Mouelhi, MD,
Novartis Institutes for Biomedical Research, East Hanover, NJ, USA

Mara Fornaro, PhD,
Novartis Institutes for Biomedical Research, Basel, Switzerland

Olivier Petricoul, PhD,
Novartis Institutes for Biomedical Research, Basel, Switzerland

Corresponding author: Christopher Grunseich, MD, Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, NIH 35-2A1010, 35 Convent Drive, Bethesda, MD 20892-3705, USA, Ph: 1-301-402-5423, christopher.grunseich@nih.gov.
*All members of the group are listed in the appendix

Contributors

RM, TS, DJG, MF, OP, IV, RR, MNM, and KHF contributed to study design. CG, RM, TS, MEM, MF, AK, JV, GS, TM, AL, JTK, and KHF contributed to data acquisition. RM, TS, MEM, RR and MNM contributed to data quality assurance and data quality analysis. CG, RM, TS, MEM, MF, MSB, and KHF contributed to data analysis. CG, RM, TS, RDG, MSB, and KHF drafted the manuscript and all authors critically revised the manuscript. All authors gave final approval for publication.

Declaration of interests

Drs. Glass and Fischbeck were named as co-inventors on a provisional patent application by Novartis pertaining to the use of IGF-1 related compounds as therapeutic agents in patients with SBMA. Drs. Glass and Fornaro are co-inventors on a patent of BVS857. Ram Miller, Therese Swan, David J Glass, Mohamed El Mouelhi, Mara Fornaro, Olivier Petricoul, Igor Vostiar, Ronenn Roubenoff, and Matthew N Meriggioli are employees of Novartis Institutes for Biomedical Research. All other authors declare that they have no conflicts of interest.

Data sharing

The study sponsor, Novartis Institutes for Biomedical Research, is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents. The requests are reviewed and approved by the sponsor's independent review panel on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com. A signed data sharing agreement is required before data access can be provided. Data will be made available with publication.

Igor Vostiar, PhD,
Novartis Institutes for Biomedical Research, Basel, Switzerland

Ronenn Roubenoff, MD,
Novartis Institutes for Biomedical Research, Basel, Switzerland

Matthew N Meriggioli, MD,
Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA

Angela Kokkinis, BSN,
Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD, USA

Robert D Guber, BS,
Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD, USA

Maher S Budron, BS,
Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD, USA

John Vissing, MD,
Copenhagen Neuromuscular Center, Department of Neurology, Righospitalet, University of Copenhagen, Denmark

Gianni Soraru, MD,
Department of Neuroscience, University of Padova, Italy

Tahseen Mozaffar, MBBS,
University of California Irvine, ALS and Neuromuscular Center, Orange, CA, USA

Albert Ludolph, MD,
Department of Neurology, University of Ulm, Germany

John T Kissel, MD,
Department of Neurology, Wexner Medical Center, Ohio State University, Columbus, OH, USA

Kenneth H Fischbeck, MD, and
Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD, USA

the BVS857 Study Group[*]

Summary

Background—Spinal and bulbar muscular atrophy (SBMA) is an X-linked neuromuscular disease caused by CAG repeat expansion in the androgen receptor (AR) gene. We assessed safety, tolerability, and preliminary efficacy of BVS857, an insulin like growth factor-1 (IGF-1) mimetic, in SBMA patients. SBMA patients have low IGF-1 levels, and studies of IGF-1 showed benefit in a transgenic model of SBMA. A study of BVS857 in healthy volunteers showed it to be well tolerated.

Methods—This was a randomized, double-blind, and placebo-controlled study in SBMA patients recruited at neuromuscular centers in Denmark (Copenhagen), Germany (Ulm), Italy (Padova), and three sites within the US (Bethesda, MD; Irvine, CA; and Columbus, OH). Eligible patients were age 18 years or older with a confirmed genetic diagnosis of SBMA, ambulatory, with symptomatic weakness, and serum IGF-1 levels of ≤ 170 ng/mL. Patients gave written informed consent before study entry. Following a safety and tolerability evaluation with 8 SBMA patients, BVS857 was administered weekly (0·06 mg/kg i.v.) for 12 weeks to 27 patients, with 2:1 drug to placebo randomization by a number scheme. Patients, investigators, and study personnel were masked to treatment assignment. Primary outcome measures included safety, tolerability, and the effects of BVS857 on thigh muscle volume (TMV) by magnetic resonance imaging. For the primary outcome measure of TMV, the ratio of post-baseline to baseline at week 13 was analyzed by analysis of covariance (ANCOVA) per protocol. An institutional review board or independent ethics committee at each site approved the study. This trial was registered with ClinicalTrials.gov, NCT02024932

Findings—31 patients were assessed for eligibility, 27 of whom were randomly assigned to either BVS857 treatment (n=18) or placebo (n=9), and 24 were included in the preliminary efficacy analysis (BVS857 group, n=15; placebo group, n=9). BVS857 was generally safe with no serious adverse events. No significant differences were found in adverse events between the BVS857 and placebo groups. Immunogenicity was detected in 13 (72%) of 18 patients in the BVS857 group, including crossreacting antibodies with neutralising capacity to endogenous IGF-1 in five patients. TMV decreased from baseline to day 85 in the placebo group (–3·4% [–110 cm3]) but not in the BVS857 group (0% [2 cm3]). A significant difference in change in TMV was observed in the BVS857 group versus the placebo group (geometric-mean ratio 1·04 [90% CI 1·01–1·07]; p=0·02). There were no differences between groups in measures of muscle strength and function.

Interpretation—TMV remained stable in BVS857 treated SBMA patients after 12 weeks of dosing. The intervention was associated with high incidence of immunogenicity and did not improve muscle strength or function. Additional studies may be needed to evaluate the efficacy of activating the IGF-1 pathway in SBMA.

Introduction

Spinal and bulbar muscular atrophy (SBMA), or Kennedy disease, is an X-linked, adult onset neuromuscular disease caused by an expanded CAG trinucleotide repeat in the androgen receptor (AR) gene.[1] The resulting polyglutamine tract expansion in the mutant AR protein produces degeneration in muscle and lower motor neurons of the brain stem and spinal cord.[2] SBMA patients typically present with weakness in the lower extremities, cramping, and tremor.[2,3] Clinical manifestations of SBMA likely arise from both toxicity of mutant AR and a loss of normal AR function.[4]

Previous controlled clinical trials evaluating the effectiveness of dutasteride and leuprorelin have had mixed results.[5–8] Cell and mouse studies have shown that insulin-like growth factor 1 (IGF-1) stimulates Akt mediated phosphorylation of the AR which enhances its clearance and ameliorates the disease phenotype.[9,10] Overexpression and administration of IGF-1 rescue histopathological and behavioral defects in transgenic mice expressing mutant

AR.[10,11] Exercise has been shown to increase IGF-1 synthesis and its anabolic effects on muscle, which were potential targets in clinical trials evaluating exercise in SBMA.[12–14] Although exercise was not found to have an effect on IGF-1 levels in SBMA, directly targeting the IGF-1 pathway may be a beneficial therapeutic strategy.[14]

IGF-1 administration has been studied in previous clinical trials of neuromuscular diseases, including a 2-year clinical trial of IGF-1 administration finding no benefit in patients with ALS.[15] A limitation of that study and others was likely the short half-life (10–30 minutes) of IGF-1,[16,17] which precludes giving sufficiently high doses without causing hypoglycemia. BVS857 was developed as a pegylated IGF-1 mimetic capable of IGF-1 receptor activation with a longer half-life, and was shown to be well tolerated in a phase 1 study of insulin-sensitive and insulin-resistant healthy participants, up to and including 0·1 mg/kg i.v. as a single dose. The pharmacokinetics of BVS857 in this phase 1 study were found to be approximately dose proportional, with a terminal elimination half-life of about 70 hours. Two participants developed acute transient facial neuropathy (Bell's palsy) at the highest dose; otherwise the adverse effect profile was acceptable.

In targeting the IGF-1 pathway in SBMA we aimed to replenish the reduced IGF-1 levels found in the disease, to stimulate downstream Akt activity to reduce the toxicity of the mutant AR,[9] and to increase anabolic activity to prevent muscle loss.[11,18] This study investigated the safety, tolerability, and preliminary efficacy of BVS857 in patients with SBMA.

Methods

Part A - Safety of BVS857 in SBMA

The study had two parts, A and B (figure 1). Two cohorts of participants with SBMA were enrolled in part A. Cohort 1 was an open-label, dose-escalation study with 2 participants, with interim analysis to assess safety and tolerability. BVS857 was administered at weeks 1 (0·01 mg/kg, intravenously [i.v.]), 3 (0·01 mg/kg, subcutaneously [s.c.]), 5 (0·03 mg/kg, s.c.), 7 (0·06 mg/kg, s.c.), and 9 (0·10 mg/kg, s.c.). Blood samples were collected for assessment of safety, pharmacokinetics (PK), and pharmacodynamics (PD). Participants returned to the study site 7 days post-dosing for assessment.

Cohort 2 was a double-blind, placebo-controlled, randomized study with 6 participants (4 BVS857, and 2 placebo). The cohort also received escalating doses at weeks 1 (0·03 mg/kg, i.v.), 3 (0·03 mg/kg, s.c.), 5 (0·06 mg/kg, s.c.), 7 (0·10 mg/kg, s.c.), and 9 (0·10 mg/kg, s.c. at higher concentration).

The safety measurements included physical and neurological exams, electrocardiograms, vital signs, standard clinical laboratory evaluations, glucose monitoring, adverse event (AE) logs, IGF-1 levels, facial photography, fundus exam, visual acuity, and detection of binding and neutralizing antibodies for endogenous IGF-1 and BVS857. Adverse events were reported continuously during the study as specified in the protocol. The total IGF-1 equivalency was defined as a value equal to the serum endogenous IGF-1 level plus 0·2 times the serum BVS857 concentration (both in molar units), to account for the potency

difference between endogenous IGF-1 versus BVS857 (1/5th of endogenous IGF-1). A safety cut-off for total IGF-1 equivalency of 400 ng/mL was set at an arbitrary threshold providing > 3-fold safety margin compared to the maximum total IGF-1 equivalency previously associated with the two cases of Bell's palsy in the phase 1 study in healthy volunteers with normal serum IGF-1 levels.

Serum concentrations of BVS857 and endogenous IGF-1 were determined by a validated sandwich enzyme-linked immunosorbent assay (ELISA). This validated PK assay enabled selective quantification of BVS857 in human serum in the presence of endogenous IGF-1 with lower limit of quantification of 12.2 ng/mL. Validated ELISA assays were also used for the determination of binding anti-BVS857 and anti-IGF-1 antibodies in human serum. Samples confirmed positive for binding antibodies were further subjected to assessment of neutralizing capacity against BVS857 and endogenous IGF-1. Validated cell-based assays combined with sequential ELISA-based assay step were used for confirmation of neutralizing capacity. Samples confirmed positive for binding anti-BVS857 were also checked for antibody cross-reactivity with the polyethylene glycol (PEG) moiety or endogenous IGF-2 using validated ELISA assays.

Biomarker measurements included thigh muscle volume (TMV) and muscle biopsy for histology and biochemistry. IGF-1 level comparisons to controls were calculated using the age-corrected standard deviation score (SDS) against a published group of healthy control males[19], with all values obtained using a Seimens Immulite 2000.

Part B - Safety and Preliminary Efficacy

Part B was comprised of cohorts 3, 4, and 5. Participants were not enrolled in the subcutaneous dosing Cohort 3 given the low systemic bioavailability with this route of administration. The first two participants in the open label portion (Cohort 4) received BVS857 0·1 mg/kg i.v. for three doses and were withdrawn early because the total IGF-1 equivalency threshold of 400 ng/mL was exceeded. For the remainder of part B, participants in Cohort 5 received 12 weekly doses of BVS857 at 0·06 mg/kg (with a maximum of 6 mg) i.v. or placebo. TMV measurements were collected by MRI at baseline, 6 weeks, and one week after the last dose of the study drug. Safety measurements were assessed in all phases of the study.

Patients

Participants were recruited in Denmark (Copenhagen), Germany (Ulm), Italy (Padova), and three sites within the US (Bethesda, MD; Irvine, CA; and Columbus, OH). Written informed consent was provided from all participants before enrollment. Enrollment was from February 2014 to December 2015. The inclusion criteria for participation in the study required participants to be at least 18 years of age and have genetically confirmed SBMA, symptomatic muscle weakness, serum IGF-1 levels less than or equal to 170 ng/ml at screening, and the ability to complete a 2-minute timed walk test with or without the aid of an assistive device at both screening and baseline. Key exclusion criteria for the study were the use of other investigational drugs at the time of enrollment; a history of Bell's palsy, raised intracranial pressure, papilledema, pseudotumor cerebi, retinopathy, or cancer (other

than non-melanomatous skin cancer, which had been completely resected); medically treated diabetes mellitus or hypoglycemia; severe facial weakness as documented by a score of 1 or 2 on items A or B of the Bulbar Rating Scale[5] at screening or baseline; or use of drugs known to affect muscle metabolism within the previous 3 months, including systemic corticosteroids (> 10 mg/day prednisone or equivalent), androgens or androgen reducing agents, systemic beta agonists or beta blockers, or relevant herbal or nutraceutical products. A full list of inclusion and exclusion criteria can be found in the appendix. The study was approved by the institutional review board or independent ethics committee at each site. The study was conducted according to the ethical principles of the Declaration of Helsinki.

Randomization and masking

Participants in cohort 2 of part A and cohort 5 of part B were randomly assigned, 2:1 drug to placebo, to treatment groups using allocation cards produced by Novartis that were unbiased and concealed from patients and staff. The 2:1 randomization was chosen to achieve clinical equipoise and appropriately balance the risk:benefit ratio between the treatment and placebo groups. The site received the treatment allocation cards and then contacted the clinical trial leader for assignment of the randomization number. The study drug and the placebo were identical in appearance, labeling, and administration schedule once reconstituted by an unblinded pharmacist. The participants, investigators, and study personnel remained blinded to the treatment of the participants.

Study drug

The study drug BVS857 is a human IGF-1 mimetic that was pegylated in order to increase its half-life, and modified to protect it from inhibition by IGF binding proteins. BVS857 was modified to have less proteolytic cleavage than the native form and decreased binding to the inhibitor IGFBP5, and pegylated at the N-terminus (supplemental figure 1). The drug was reconstituted at each of the study sites and prepared for each participant before dosing.

Outcomes

The objective of the study was to evaluate the safety, tolerability, and efficacy of BVS857 in SBMA. Change in the TMV by MRI from baseline to day 85 was used as the primary outcome measurement for efficacy because of the expected effect of BVS857 on muscle, and its utility in detecting muscle volume changes in a previous study of patients with a low average volume error.[20] Thigh muscle images were obtained locally by MRI, and analyzed centrally by VirtualScopics (Rochester, NY) in a blinded fashion. VirtualScopics oversaw the training of MRI technicians to ensure images collected at all study sites used the same procedures. VirtualScopics also performed all quality control assessments and volumetric determination of the MRI images. Secondary outcome measures included the Adult Myopathy Assessment Tool (AMAT)[21], lean body mass through DXA, and BVS857 PK. Prespecified exploratory outcomes included quantitative muscle testing (QMT), Timed Up and Go, 2 or 6 min walk test, the Bulbar Rating Scale, BVS857 immunogenicity, quality of life questionnaires (SF-36 Physical and Mental Component Scores and EQ-5D), serum IGF-1 levels, safety markers, and MRI of subcutaneous adipose tissue and intramuscular adipose tissue.

Statistical analysis

The sample size for part A was arbitrarily selected for an initial evaluation of safety that would allow an 80% chance for detecting an AE with an occurrence rate of 24% to be observed at least once. For part B, the sample size was selected to detect a change in TMV of at least 5% from baseline to week 13 with a power of over 85%.[20] For the TMV primary and other outcome measures, the log-transformed ratio of post-baseline to baseline at day 85 was analyzed using an ANCOVA model containing terms of treatment as fixed effect and log-transformed baseline as a covariate. All participants who had missing data points from either baseline or from day 85 were excluded from the ANCOVA analysis. The 90% confidence interval was derived by back-transformation to the original scale. For the TMV, a 1-sided p-value was calculated representing the upper tailed test. We declared efficacy of treatment if at day 85 (week 13), the null hypothesis (Ho): $\Delta=1$ vs. Alternative hypothesis (HA): $\Delta \geq 1$ was rejected at alpha=0·1. This proof of concept study was exploratory in nature, and not intended to be confirmatory. The type-1 error rate was deliberately chosen to minimize the likelihood of a false negative result so that the risk of rejecting a potentially valuable program at this early stage is reduced. The Data Monitoring Committee provided unmasked analysis of patient safety data and BVS857 serum levels. Statistical analysis for ANCOVA was done using SAS software. The trial was registered with ClinicalTrials.gov, NCT02024932.

Role of the funding source

The authors maintained sole control over the study design, execution, analysis, and interpretation. The investigators had free and unrestricted access to the data, and all authors participated in the writing and final decision to submit this work for publication. The sponsor and funding organisation collaborated in the writing of the report and the decision to submit for publication.

Results

Eight study participants in cohorts 1 and 2 were enrolled in part A of the study (table 1, figure 1). All participants had total IGF-1 levels below 170 ng/ml, consistent with measurements from other SBMA patients (supplemental figure 2). Both participants in the open-label cohort 1 were discontinued before study completion due to mild erythema at the injection site that was well tolerated. The study drug concentration and number of injections were adjusted for cohort 2; nevertheless 3 of 4 participants randomized to BVS857 had similar injection site reactions that resulted in discontinuation, with no reactions in the control group (supplemental table 1). Overall, the injection site erythema resulted in the discontinuation of study drug for 5 of 6 (83%) participants in cohorts 1 and 2. There were no study drug related trends in any clinical laboratory safety evaluations (hematology, clinical chemistry, urinalysis), vital signs, physical examinations, or any other related safety observations. In cohort 2, one participant in the placebo group had neutralizing antibodies to BVS857 at day 1 of the study. The PK measurement of BVS857 in the serum showed low systemic bioavailability with high inter-individual variability and an apparent lack of dose proportionality with s.c. dosing (data not shown).

The low and variable exposure of BVS857 along with the high incidence of injection site erythema following s.c. administration led to the decision to switch to an i.v. infusion for part B. A 2-subject open-label phase was done to evaluate the PK and safety of an i.v. dose of 0·1 mg/kg BVS857 administered weekly (part B cohort 4). After the interim/safety analysis it was determined that the dose resulted in elevation above the 400 ng/mL cut-off for the total IGF-1 equivalence. No AEs were reported in this open-label cohort, however the elevated active IGF-1 equivalence resulted in early termination of that cohort.

Following the open-label safety phase, the BVS857 dose was reduced by 40%, to 0·06 mg/kg weekly i.v. for the final phase of the study (supplemental figure 3). 27 patients were randomized for this placebo-controlled, double-blinded phase. The demographic information for participants, including CAG repeat length, is summarized in table 1. Two participants did not complete the study due to contact dermatitis (not attributed to the study drug) and hypersensitivity reaction with urticaria that resolved following diphenhydramine (figure 1). The remaining 25 participants (16 on BVS857, and 9 on placebo) were compliant in dosing and completed the study at 13 weeks (85 days). Most participants on placebo (89%) and BVS857 (94%) reported an AE, with a higher percentage of participants in the BVS857 group having moderate AEs compared to the placebo group (table 2). The most common AE was nasopharyngitis, reported in 4 participants on BVS857 and 1 on placebo. Muscle weakness and fatigue were each reported in 2 patients on BVS857, but not on placebo. Administration of BVS857 resulted in no serious AEs. Also, there were no trends associated with treatment in safety measurements of hepatic and renal function obtained from blood and urine. Participants on BVS857 did not have any significant change in CK, LDH, lipase, amylase, triglycerides, total cholesterol, or liver enzymes. No participants developed hypoglycemia or Bell's palsy, which may be associated with supraphysiologic IGF-1 pathway activation. Overall the drug was well tolerated.

BVS857 had expected PK following repeated i.v. administration, with no evidence of systemic accumulation (supplemental figure 4). The average Cmax and Tmax in part B were 788 ng/mL (range 368 – 3430 ng/mL) and 1.9 hours (range 1·0 – 4·4 hours). This rise in the serum level of BVS857 resulted in an increase in the total IGF-1 equivalency, which peaked at 1 hour and declined to baseline levels over 48 hours (supplemental figure 5A). We did not detect a correlation between percent change in IGF-1 equivalency (average of days 1, 36, and 78) and percent change in TMV in those patients receiving BVS857 (appendix). An increase in IGFBP2 was detected at 4 hours post drug delivery (supplemental figure 5B). No significant changes were observed in IGFPB3 or IGFBP5 levels as a result of BVS857 treatment (data not shown). Variability in the quality of the collected muscle biopsy samples limited the ability to accurately determine AR protein aggregation and levels, Akt signaling, and muscle fiber cross-sectional area.

The percent change in TMV from baseline to day 85 was significantly different in the BVS857 group compared to the placebo group (p=0·02, one-tailed ANCOVA; geometric-mean ratio 1·04, 90% confidence interval 1·01, 1·07). The TMV remained stable in the BVS857 group and decreased in the placebo group over the course of the treatment period (figure 2, table 3). Follow-up TMV measurements at 106 days showed a similar change, although not significant (p=0·08), which decreased at 134 days (p=0·11). Three participants

in the BVS857 group were prospectively excluded from the day 85 analysis due to the quality of the MRI images obtained.

Improvement in the AMAT score was seen in both the placebo (7·0%) and the BVS857 (4·9%) groups from baseline to day 85, but there was no significant difference between them (table 3). There was neither a significant difference nor a change in the lean body mass of participants in both the placebo and BVS857 groups at day 85 compared to baseline (table 3). There was a significant increase from baseline (p=0·04) of the geometric-mean ratio (1·05) for subcutaneous adipose tissue in the BVS857 group at day 85 as compared to placebo (supplemental table 2). There was a positive change over time in the EQ-5D in both the placebo and BVS857 groups that did not reach statistical significance, and a significant difference in the SF-36 Mental Component Score with BVS857 (p=0·03) (supplemental table 2). Overall, there was no significant difference in any of the motor functional measures between the BVS857 and placebo groups. We did not detect a significant increase in Akt signaling in monocytes, strength of the quadriceps or hamstring muscles, or other functional muscle testing.

Two participants (11%) had pre-existing binding anti-BVS857 antibodies before initiation of the treatment with BVS857. Neither patient had been previously exposed to BVS857. In one case, the pre-existing antibodies were cross-reactive with endogenous IGF-1, but not neutralizing. Over the course of treatment more than half of the participants on BVS857 developed antibodies against BVS857. A total of 13 participants in part B developed antibodies, which were neutralizing against BVS857 in 6 participants (table 4). Anti-BVS857 antibody titers reached their maximum after completion or discontinuation of treatment (typically after day 85) and gradually declined thereafter in all cases. Four participants developed antibodies to PEG, and eight participants developed antibodies against endogenous IGF-1. Of these eight, five participants developed neutralizing antibodies to endogenous IGF-1. One participant developed a hypersensitivity reaction after the second dose of the study agent and was discontinued from the study. After discontinuation, this participant was found to have neutralizing antibodies to endogenous IGF-1, which subsequently resolved in samples tested three and four months after the end of study visit. A second participant was also found to have neutralizing antibodies to endogenous IGF-1 at the end of study, which similarly resolved during testing three and four months after the end of study visit. No participants in the placebo group developed BVS857 or IGF-1 antibodies, and no participants in the BVS857 group developed antibodies that cross-reacted with IGF-2. Onset of immunogenicity had no apparent impact on the pharmacokinetics of BVS857.

Discussion

This study met its primary outcome measure and showed that there was a significant difference in thigh muscle volume at 85 days between the BVS857 and placebo groups. The participants receiving BVS857 did not lose TMV, while the placebo group showed a decline in TMV. BVS857 did not result in improvement in measures of muscle strength or function. In all cohorts of the study BVS857 was well tolerated, with no evidence of hypoglycemia, Bell's palsy, or serious AEs[15,22].

Previous clinical trials in SBMA targeted the activity of the AR by either reducing the production of testosterone[5,6,8] or reducing the conversion of testosterone to dihydrotestosterone[7]. Other candidate approaches aim to reduce the mutant AR by promoting its degradation, decreasing its expression, or activating pathways which have the capacity to increase the clearance of the mutant AR or have direct trophic effects on muscle tissue.

The rationale for using BVS857 in this setting includes the finding of reduced IGF-1 levels in SBMA patients. Correcting this loss of IGF-1 activity could help to mitigate the disease. IGF-1 treatment in SBMA mice has been shown to ameliorate disease toxicity by both transgenic overexpression and exogenous administration.[10,11] IGF-1 activity produces benefit by activating Akt signaling, which promotes the clearance of the mutant AR, and through its direct trophic effect on muscle tissue.[23,24] Akt signaling can also be increased by β-agonist administration.[25] Clenbuterol is a β-agonist that has shown signs of efficacy in both an animal model and a small human pilot clinical trial in SBMA.[25–27] The phosphorylation of Akt by clenbuterol in mice and patient-derived myotubes was accompanied by a significant increase in myotube size and a reduction of AR protein expression with treatment.[26] In our study we did not observe an increase in Akt signaling in monocytes or muscle biopsy samples, a downstream marker of IGF-1 activity. The absence of any measured affect on Akt signaling may be a consequence of the relatively short duration of the increase in total IGF-1 equivalency.

We did not observe a significant difference in the quality of life for patients with SBMA in the EQ-5D thermometer score or the SF-36 quality of life survey. Both the placebo and the BVS857 groups showed signs of improvement, although a significant change in SF-36 Mental Component Score was seen in the BVS857 group only. These changes indicate that participants may be more positive about their quality of life as participants in a study. Previous studies with dutasteride reported a significant increase in the physical component score of the SF-36, along with a decrease in the mental component score compared to placebo.[7] The development of a quality of life measurement tool specific to SBMA may provide the opportunity to identify changes in participants' perceived health status.[28]

The prespecified exploratory outcome of subcutaneous adipose tissue measurement showed a significant increase in the amount of fat in those receiving BVS857, while there was no significant difference in the intramuscular fat or lean body mass. A study in mice has shown that increasing the subcutaneous adipose tissue can be beneficial, due to the shift in fat deposition away from liver and muscle and improvement in insulin sensitivity.[29] Reductions in IGF-1 have been shown to play a role in peripheral insulin resistance, and a recent report in 55 males showed signs of insulin resistance based on the homeostasis model assessment.[30] Although it is not certain that this change in subcutaneous adipose tissue is a result of the study drug, the effects on metabolic function should be considered in future studies of the IGF-1 pathway in SBMA.

In conclusion, BVS857 had a significant effect on TMV, the primary outcome measure, in patients with SBMA after 12 weeks of weekly administration. The high degree of reproducibility with this imaging tool allowed us to determine biological effect of the

intervention in a relatively small number of patients over a short period of time, and we believe that has implications for other clinical proof of concept studies in patients with muscle atrophy or wasting. However, the change in TMV was not accompanied by a change in measures of muscle strength and function. The absence of a change in muscle function may be a consequence of the relatively small effect on muscle volume. Also, the study was not specifically powered to detect changes in muscle function, where the measures have greater variability and a longer period of treatment may be required. BVS857 had PD effects in increasing IGFBP2 and decreasing endogenous IGF-1, although the IGF-1 receptor biomarker phosphorylated Akt did not show a change, and levels of mutant AR protein in muscle, which decreased in the animal studies, could not be reliably determined in the human samples.

BVS857 was developed to have an improved half-life compared to endogenous IGF-1 and reduced binding to inhibitory binding proteins, the combination of which would be expected to have longer lasting activity on the muscle compared to IGF-1 administration. Although the half-life of BVS857 (~24 hrs) in SBMA participants is an improvement over exogenous IGF-1 delivery (0·5 hrs)[16,17], the half-life was less than that observed in the healthy volunteer phase 1 study (70 hrs). It is possible that the relatively short half-life of BVS857 in SBMA patients limited our ability to maintain appropriate BVS857 exposure level over the weekly dosing interval and thus to detect an improvement in muscle function. Future IGF-1 mimetics will likely need an improved half-life to achieve the desired pharmacological effects with similar or less frequent dosing. Additionally, we observed neutralizing antibodies against endogenous IGF-1 which could have a deleterious effect on the pathway it is intended to activate, although no pharmacokinetic or clinical consequences were observed in these study patients or reported in children taking recombinant IGF-1 who developed IGF-1 antibodies.[31] The evidence of prelmininary efficacy over the short time frame of 12 weeks in this study is encouraging and not previously described.[5,6,7] We anticipate that a trial with sufficient power and longer duration would be needed to evaluate muscle strength and function. Activation of the IGF-1 pathway by other means, perhaps in combination with an anti-androgen agent, may be worth pursuing in future clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Novartis Pharmaceuticals was the sponsor of this study and developed and provided the study agent and placebo, assisted with data collection and analysis, and provided safety monitoring. The study was also supported by NINDS intramural research funds. We thank Elizabeth Hartnett, George Harmison, and Ke-lian Chen (NINDS, National Institutes of Health) for their help in sample processing and scheduling during the study, the clinical staff (appendix) across all of the study sites (University of Copenhagen, Copenhagen, Denmark; University of Padova, Padua, Italy; University of California Irvine, ALS and Neuromuscular Center, Orange, CA 92868, USA; University of Ulm, Ulm, Germany; Ohio State University, Columbus, OH, USA; and National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD 20892, USA), and the patients who made this study possible.

Funding

Novartis Pharmaceuticals and the US National Institutes of Health.

References

1. La Spada AR, Wilson EM, Lubahn DB, Harding AE, Fischbeck KH. Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. Nature 1991; 352: 77–9. [PubMed: 2062380]
2. Rhodes LE, Freeman BK, Auh S, et al. Clinical features of spinal and bulbar muscular atrophy. Brain 2009; 132: 3242–51. [PubMed: 19846582]
3. Atsuta N, Watanabe H, Ito M, et al. Natural history of spinal and bulbar muscular atrophy (SBMA): a study of 223 Japanese patients. Brain 2006; 129: 1446–55. [PubMed: 16621916]
4. Dejager S, Bry-Gauillard H, Bruckert E, et al. A comprehensive endocrine description of Kennedy's disease revealing androgen insensitivity linked to CAG repeat length. J Clin Endocrinol Metab 2002; 87: 3893–901. [PubMed: 12161529]
5. Banno H, Katsuno M, Suzuki K, et al. Phase 2 trial of leuprorelin in patients with spinal and bulbar muscular atrophy. Ann Neurol 2009; 65: 140–50. [PubMed: 19259967]
6. Katsuno M, Banno H, Suzuki K, et al. Efficacy and safety of leuprorelin in patients with spinal and bulbar muscular atrophy (JASMITT study): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurol 2010; 9: 875–84. [PubMed: 20691641]
7. Fernández-Rhodes LE, Kokkinis AD, White MJ, et al. Efficacy and safety of dutasteride in patients with spinal and bulbar muscular atrophy: a randomised placebo-controlled trial. Lancet Neurol 2011; 10: 140–47. [PubMed: 21216197]
8. Hashizume A, Katsuno M, Suzuki K, et al. Long-term treatment with leuprorelin for spinal and bulbar muscular atrophy: natural history-controlled study. J Neurol Neurosurg Psychiatry 2017; 0: 1–7.
9. Palazzolo I, Burnett BG, Young JE, et al. Akt blocks ligand binding and protects against expanded polyglutamine androgen receptor toxicity. Hum Mol Genet 2007; 16: 1593–603. [PubMed: 17470458]
10. Palazzolo I, Stack C, Kong L, et al. Overexpression of IGF-1 in muscle attenuates disease in a mouse model of spinal and bulbar muscular atrophy. Neuron 2009; 63: 316–28. [PubMed: 19679072]
11. Rinaldi C, Bott LC, Chen KL, Harmison GG, Katsuno M. Insulinlike growth factor (IGF)-1 administration ameliorates disease manifestations in a mouse model of spinal and bulbar muscular atrophy. Mol Med 2012; 18: 1261–68. [PubMed: 22952056]
12. Preisler N, Andersen G, Thøgersen F, Crone C, Jeppesen TD, Vissing J. Effect of aerobic training in patients with spinal and bulbar muscular atrophy (Kennedy disease). Neurology 2009; 72: 317–323. [PubMed: 19171827]
13. Schwarz AJ, Brasel JA, Hintz RL, Mohan S, Cooper DM. Acute effect of brief low- and high-intensity exercise on circulating insulin-like growth factor (IGF) I, II, and IGF-binding protein-3 and its proteolysis in young healthy men. J Clin Endocrinol Metab 1996; 81: 3492–97. [PubMed: 8855791]
14. Shrader JA, Kats I, Kokkinis A, et al. A randomized controlled trial of exercise in spinal and bulbar muscular atrophy. Ann Clin Transl Neurol 2015; 2: 739–47. [PubMed: 26273686]
15. Sorenson EJ, Windbank AJ, Mandrekar JN, et al. Subcutaneous IGF-1 is not beneficial in 2-year ALS trial. Neurology 2008; 71: 1770–75. [PubMed: 19029516]
16. Yakar S, Rosen CJ, Beamer WG, et al. Circulating levels of IGF-1 directly regulate bone growth and density. J Clin Invest 2002; 110: 771–81. [PubMed: 12235108]
17. Guler HP, Zapf J, Schmid C, Froesch ER. Insulin-like growth factors I and II in healthy man. Estimations of half-lives and production rates. Acta Endocrinologica 1989; 121: 753–58. [PubMed: 2558477]
18. Rommel C, Bodine SC, Clarke BA, et al. Mediation of IGF-1-induced skeletal myotube hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathways. Nat Cell Biol 2001; 3: 1009–13. [PubMed: 11715022]
19. Colao A, Di Somma C, Cascella T, et al. Relationship between serum IGF-1 levels, blood pressure, and glucose tolerance: an observational, exploratory study of 404 subjects. Eur J Endocrinol 2008; 159: 389–97. [PubMed: 18603571]

20. Amato AA, Sivakumar K, Goyal N, et al. Treatment of sporadic inclusion body myositis with bimagrumab. Neurology 2014; 83: 2239–46. [PubMed: 25381300]
21. Harris-Love MO, Fernandez-Rhodes L, Joe G, et al. Assessing function and endurance in adults with spinal and bulbar muscular atrophy: validity of the adult myopathy assessment tool. Rehabil Res Pract 2014; 2014: 873872. [PubMed: 24876969]
22. Jacob R, Barrett E, Plewe G, Fagin KD, Sherwin RS. Acute effects of insulin-like growth factor I on glucose and amino acid metabolism in the awake fasted rat. Comparison with insulin. J Clin Invest 1989; 83: 1717–23. [PubMed: 2651479]
23. Rommel C, Bodine SC, Clarke BA, et al. Mediation of IGF-1-induced skeletal myotube hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathways. Nature Cell Biology 2001; 3: 1009–13. [PubMed: 11715022]
24. Lai K-MV, Gonzalez M, Poueymirou WT, et al. Conditional Activation of Akt in Adult Skeletal Muscle Induces Rapid Hypertrophy. Mol Cell Biol 2004; 24: 9295–304. [PubMed: 15485899]
25. Joassard OR, Durieux A-C, Freyssenet DG. β2-Adrenergic agonists and the treatment of skeletal muscle wasting disorders. Int J Biochem Cell Biol 2013; 45: 2309–21. [PubMed: 23845739]
26. Milioto C, Malena A, Maino E, et al. Beta-agonist stimulation ameliorates the phenotype of spinal and bulbar muscular atrophy mice and patient-derived myotubes. Sci Rep 2017; 7: 41046. [PubMed: 28117338]
27. Querin G, D'Ascenzo C, Peterle E, et al. Pilot trial of clenbuterol in spinal and bulbar muscular atrophy. Neurology 2013; 80: 2095–98. [PubMed: 23645595]
28. Guber RD, Kokkinis AD, Schindler AB, et al. Patient-identified impact of symptoms in spinal and bulbar muscular atrophy. Muscle Nerve 2018; 57: 40–44. [PubMed: 28877556]
29. Kim J-Y, van de Wall E, Laplante M, et al. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. J Clin Invest 2007; 117: 2621–37. [PubMed: 17717599]
30. Nakatuji H, Araki A, Hashizume A, et al. Correlation of insulin resistance and motor function in spinal and bulbar muscular atrophy. J Neurol 2017; 264: 839–47. [PubMed: 28229243]
31. Chernausek SD, Backeljauw PF, Frane J, et al. Long-term treatment with recombinant insulin-like growth factor (IGF)-1 in children with severe IGF-1 deficiency due to growth hormone insensitivity. J Clin Endocrinol Metab 2007; 92: 902–10. [PubMed: 17192294]

Research in context

Evidence before this study

A review of the literature with PubMed was done for clinical trials published before June 1, 2018 with the search terms “spinal bulbar muscular atrophy”, “Kennedy’s disease”, “spinal and bulbar muscular atrophy”, “spinobulbar muscular atrophy”, and “bulbospinal muscular atrophy” without language restriction. The review showed that three randomized, placebo-controlled therapeutic trials in patients with spinal and bulbar muscular atrophy (SBMA) have been previously published, evaluating the androgen-reducing reagents leuprorelin and dutasteride. These studies did not show benefit in the primary outcome measures of muscle strength and swallowing during the time period examined, although indications of efficacy were observed in secondary. Previous studies have shown that insulin like growth factor-1 (IGF-1) over-expression and delivery in a transgenic mouse model rescues biochemical and motor manifestations of the disease.

Added value of this study

This double-blinded, placebo-controlled study evaluated the safety and preliminary efficacy of BVS857, an IGF-1 mimetic, in patients with SBMA. The study met its primary outcome measure of change in thigh muscle volume (TMV), with a significant difference of TMV in the BVS857 interventional arm versus placebo. No significant differences in measures of muscle strength and function were observed. The IGF-1 mimetic was generally well tolerated with no serious adverse effects, although evidence of immunogenicity was detected.

Implications of all the available evidence

The results of this trial indicate that IGF-1 pathway activation may be worth pursuing further as an approach to therapy for patients with SBMA. TMV can be considered in future studies as an imaging biomarker for muscle wasting and denervation. The immunogenicity of BVS857 limits its use as a therapeutic agent, but other activators of the IGF-1 pathway may be considered in future clinical trials.

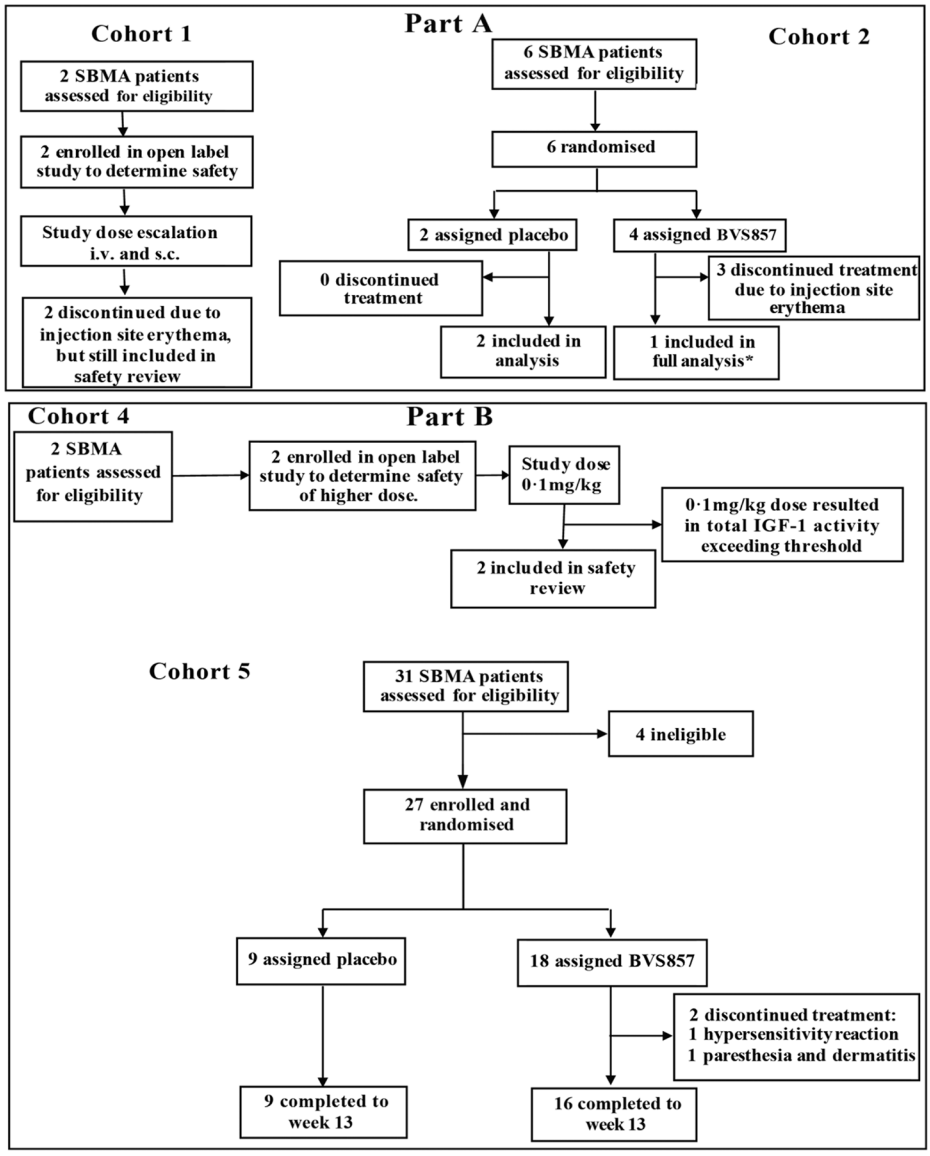

Figure 1: Trial profile

*All participants in Cohort 2 were included in safety review.

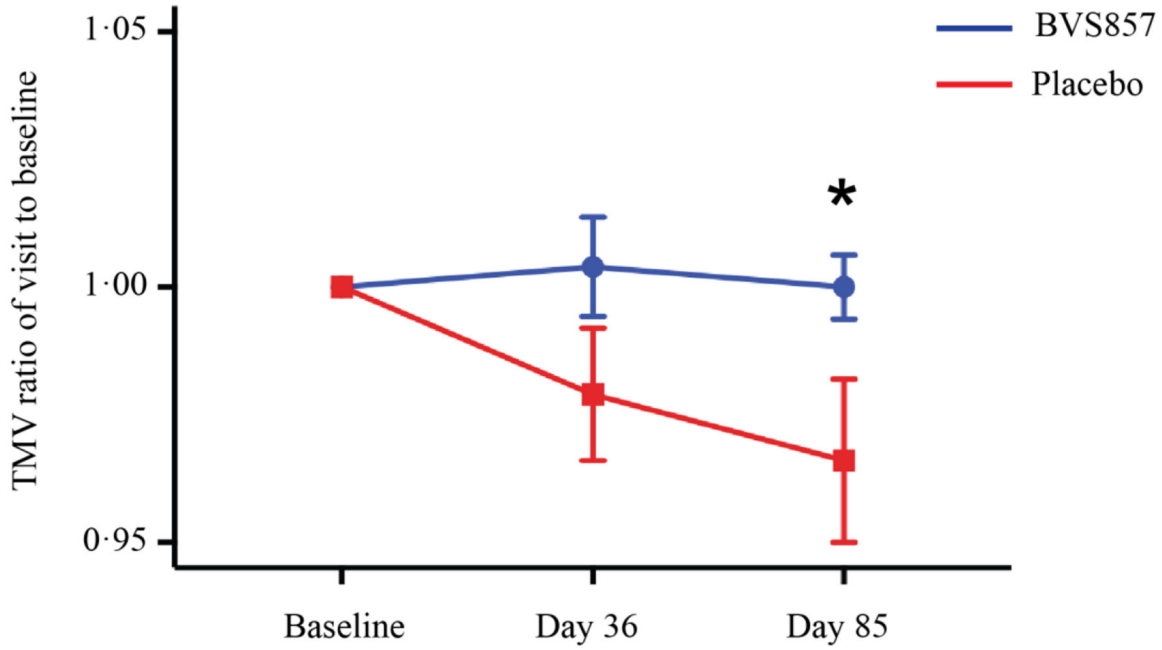

Figure 2: Effect of BVS857 on the primary outcome measure, thigh muscle volume

A significant difference in thigh muscle volume (TMV) was observed at day 85 in participants receiving BVS857 when compared to placebo. (p=0·02). Error bars indicate standard error of the mean.

Table 1:

Baseline characteristics

	Cohort 1	Cohort 2		Cohort 4	Cohort 5	
	BVS857 (n=2)	Placebo (n=2)	BVS857 (n=4)	BVS857 (n=2)	Placebo (n=9)	BVS857 (n=18)
Age [years]	67 ± 6	60 ± 8	56 ± 12	42 ± 5	54 ± 6	57 ± 12
Repeat length [# CAGs]	45 ± 1	45 ± 1	46 ± 3	50 ± 3	46 ± 5	45 ± 3
BMI [kg/m^2]	30 ± 8	N/A	24 ± 3	29 ± 3	27 ± 3	26 ± 4
CK [U/L]	550 ± 86	516 ± 16	1193± 946	1903 ± 1265	1336±778	848 ± 707
TMV (cm^3)	3383±268	2922 ± 832	2935±417	N/A	3166±882	3308 ± 764
AMAT	N/A	N/A	N/A	29 ± 1	30 ± 8	33 ± 8
2-minute walk distance [m]	116 ± 44	125 ± 74	147 ± 26	N/A	114 ± 30	135 ± 50
Bulbar rating scale [BRS]	30 ± 1	31 ± 2	31 ± 2	N/A	30 ± 2	30 ± 2
SF-36 PCS	36 ± 3	38 ± 8	36 ± 7	N/A	41 ± 8	40 ± 10
SF-36 MCS	56 ± 13	62 ± 3	53 ± 13	N/A	56 ± 9	55 ± 9

Baseline characteristics for Parts A (Cohorts 1+2) and B (Cohorts 4+5). Data are mean ± SD. CK=creatine kinase. TMV=thigh muscle volume. N/A=not available. AMAT=Adult Myopathy Assessment Tool. PCS=physical component summary. MCS=mental component summary.

Table 2:

Summary of adverse events.

	Cohort 5	
	Placebo N=9 n (%)	**BVS857 N=18 n (%)**
Participants with AE(s)	8 (89)	17 (94)
Nasopharyngitis	1 (11)	4 (22)
Headache	1 (11)	3 (17)
Back pain	2 (22)	1 (6)
Dizziness	0 (0)	2 (11)
Fatigue	0 (0)	2 (11)
Muscular weakness	0 (0)	2 (11)
Positive neutralizing antibodies	0 (0)	2 (11)
Paresthesia	0 (0)	2 (11)
Puncture site pain	0 (0)	2 (11)
Arthralgia	1 (11)	1 (6)
Erythema	1 (11)	1 (6)
Hypertension	1 (11)	1 (6)
Musculoskeletal pain	1 (11)	1 (6)
Nausea	1 (11)	1 (6)
Skin hypersensitivity	1 (11)	1 (6)
Severity		
Mild	4 (44)	5 (28)
Moderate	3 (33)	11 (61)
Severe	1 (11)	1 (6)

Adverse event frequencies from Part B only, percentages indicated in parentheses. Adverse events were not reported from the two participants in cohort 4.

Table 3:

Summary of primary and secondary outcome measures

	Placebo					BVS857					Difference in change at day 85, BVS857 vs. placebo (SE) (90% CI)
	Baseline		Day 85			Baseline		Day 85			
	n	mean ± SD	n	mean ± SD	change from baseline[#] (%)	n	mean ± SD	n	mean ± SD	change from baseline# (%)	
TMV (cm^3) (primary outcome measure)	9	3166 ± 882	9	3056 ± 866	−110 (−3·4%)	17	3308 ± 764	15	3287 ± 823	2 (0·0%)	[§]1·04 (101, 107) [*]p=0 02
AMAT	9	29·9 ± 7·7	9	32·2 ± 90	2·3 (7·0%)	18	33·0 ± 8·0	18	34·0 ± 7·2	10 (4·9%)	−0·99 (1·49) (−3·54, 1 · 57)
DXA lean body mass (kg)	8	45·0 ± 7·7	9	44·4 ± 7·9	0·16 (0·3%)	18	44·7 ± 4·4	17	45·3 ± 4·6)	0·8 (1·8%)	0·63 (0·64) (−0·46, 1·72)

Thigh muscle volume (TMV), Adult Myopathy Assessment Tool (AMAT), standard error (SE), statistic for 90% confidence interval (CI) ANCOVA (treatment as fixed effect and baseline as covariate).

[§]Geometric-mean ratio of BVS857 vs. placebo

[*]1-sided p-value from ANCOVA, as described above.

[#]Change from baseline calculated from participants with data at both baseline and day 85.

Table 4:

Frequency of immunogenicity in Part B (Cohort 5)

Visit	Treatment	Binding anti-BVS857 antibodies n/m (%)	Neutralising anti-BVS857 antibodies n/m (%)	Binding anti-IGF-1 antibodies n/m (%)	Neutralising Anti-IGF-1 antibodies n/m (%)	Anti-PEG antibodies n/m (%)
Day 1	BVS857	2/18 (11)	0/2 (0)	1/18 (6)	0/1 (0)	0/2 (0)
	Placebo	0/9 (0)	0/0 (0)	0/9 (0)	0/0 (0)	0/0 (0)
Day 36	BVS857	4/17 (24)	0/4 (0)	1/17 (6)	0/1 (0)	0/2 (0)
	Placebo	0/9 (0)	0/0 (0)	0/9 (0)	0/0 (0)	0/0 (0)
Day 78	BVS857	12/16 (75)	3/12 (25)	5/16 (31)	3/10 (30)	1/12 (8)
	Placebo	0/9 (0)	0/0 (0)	0/9 (0)	0/0 (0)	0/0 (0)
Day 85	BVS857	13/18 (72)	6/13 (46)	4/18 (22)	4/11 (36)	4/12 (33)
	Placebo	0/9 (0)	0/0 (0)	0/9 (0)	0/0 (0)	0/0 (0)
EOS	BVS857	10/15 (67)	1/10 (10)	8/15 (53)	1/9 (11)	1/8 (13)
	Placebo	0/9 (0)	0/0 (0)	0/9 (0)	0/0 (0)	0/0 (0)

n = total number of subjects which had the specified result. m = total number of participants evaluated at that visit. Percentages are indicated in parentheses.