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Efficacy and Safety of Elamipretide in Individuals With Primary Mitochondrial Myopathy: The MMPOWER-3 Randomized Clinical Trial

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ABSTRACT

Background and Objectives: Primary Mitochondrial Myopathies (PMMs) encompass a group of genetic disorders that impair mitochondrial oxidative phosphorylation, adversely impacting physical function, exercise capacity, and quality of life (QoL). Current PMM standards-of-care address symptoms, with limited clinical impact, constituting a significant therapeutic unmet need. We present data from MMPOWER-3, a pivotal, phase-3, randomized, double-blind, placebo-controlled clinical trial that evaluated the efficacy and safety of elamipretide in participants with genetically-confirmed PMM.

Methods: Following screening, eligible participants were randomized 1:1 to receive either 24weeks of elamipretide 40mg/day or placebo subcutaneously. Primary efficacy endpoints included change from baseline to Week 24 on the distance walked on the 6-minute Walk Test (6MWT), and Total Fatigue on the Primary Mitochondrial Myopathy Symptom Assessment (PMMSA). Secondary endpoints included Most Bothersome Symptom Score on the PMMSA, NeuroQoL Fatigue Short Form scores, and the Patient– and Clinician–Global Impression of PMM Symptoms.

Results: Participants (N=218) were randomized (n=109 elamipretide; n=109 placebo). Mean age was 45.6 year (64% women; 94% white). The majority of participants (n=162 [74%]) had mitochondrial DNA (mtDNA) mutations, with the remainder having nuclear DNA (nDNA)

defects. At screening, the most frequent bothersome PMM symptom on the PMMSA was tiredness during activities (28.9%). At baseline, mean distance walked on the 6MWT was 336.7±81.2 meters, mean score for Total Fatigue on the PMMSA was 10.6±2.5, and mean T-score for the Neuro-QoL Fatigue Short Form was 54.7±7.5. The study did not meet its primary endpoints assessing changes in the 6MWT and PMMSA Total Fatigue Score (TFS). Between the participants receiving elamipretide versus placebo, the difference in the Least Squares Mean (SE) from baseline to Week 24 on distance walked on the 6MWT was -3.2 (95% confidence interval,-18.7,12.3; *p*=0.69) meters and on the PMMSA Total Fatigue Score was -0.07 (95% confidence interval,-0.10,0.26; *p*=0.37). Elamipretide treatment was well-tolerated with most adverse events being mild to moderate in severity.

Discussion: Subcutaneous elamipretide treatment did not improve outcomes in the 6MWT and PMMSA TFS in patients with PMM. However, this phase-3 study demonstrated that subcutaneous elamipretide is well-tolerated.

Trial Registration Information: Trial registered with clinicaltrials.gov, Clinical Trials Identifier: NCT03323749; submitted on October 12, 2017; first patient enrolled October 9, 2017. https://clinicaltrials.gov/ct2/show/NCT03323749?term=elamipretide&draw=2&rank=9

Classification of Evidence

This study provides Class I evidence that elamipretide does not improve the 6 minute walk test or fatigue at 24 weeks compared to placebo in patients with primary mitochondrial myopathy.

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Keywords: myopathy, primary mitochondrial disease, elamipretide, exercise intolerance, primary mitochondrial myopathy

INTRODUCTION

A consensus of experts define Primary Mitochondrial Myopathies (PMMs), as a diverse group of genetically confirmed disorders of the mitochondria, affecting predominantly, but not exclusively, skeletal muscle, thereby adversely affecting physical function and quality of life [1,2]. The result is muscle weakness, muscle atrophy, limited exercise capacity, and symptoms of fatigue and pain [1,2]. PMM severity is variable but the progressive reduction in exercise capacity eventually impairs participants' ability to perform activities of daily living [3-5].

Primary mitochondrial diseases (PMDs) caused by both mitochondrial (mtDNA) and nuclear DNA (nDNA) mutations, are among the most common inherited metabolic disorders [2]. PMDs have been reported to affect at least 1 in 4300 people in the general population [6], or an estimated 40,000 total individuals in the US [6]. Because most patients with PMDs are reported to suffer from PMM, the prevalence of PMM specifically is estimated to be slightly less than the overall prevalence of all PMDs (aside from patients with Leber hereditary optic neuropathy [LHON]) who do not experience a skeletal muscle component) [6,7].

Currently, available standards of care primarily utilize dietary supplements that have limited clinical impact [8]. Therefore a significant unmet clinical need for new therapies exists [8]. However, there have been a number of historical challenges to the development of mitochondrial therapies, including the lack of a specific molecular target in mitochondria to promote ATP synthesis and a drug development process that is driven by disease-specific approaches [9].

Elamipretide is an investigational mitochondrial-targeting agent in development for treating patients with a variety of mitochondrial diseases [10-13]. Elamipretide is a water-soluble, aromatic-cationic mitochondria-targeting tetrapeptide that readily penetrates and transiently localizes to the inner mitochondrial membrane where it associates with cardiolipin to improve membrane stability and restore supercomplex formation thereby enhancing ATP synthesis in several organs including the heart, kidney, neurons and skeletal muscle, and reduce reactive oxygen species (ROS) production [10,13-26]. High resolution respirometry studies in human and animal models of myopathy have demonstrated elamipretide-mediated improvement of respiration across various electron transport chain complexes [27,28]. These effects corresponded with significantly improved mitochondrial and cristae morphology [27], which are known to be altered across many mitochondrial myopathies [29]

The elamipretide clinical development program included MMPOWER-1 and MMPOWER-2, whereby treatment with elamipretide demonstrated meaningful improvements in patient-reported outcomes (PROs) for patients with confirmed PMM [10,11]. MMPOWER-3 was a pivotal, phase 3, randomized, double-blind, placebo-controlled clinical trial designed to evaluate the efficacy and safety of elamipretide 40mg subcutaneously (SC) once daily for 24 weeks as a treatment for PMM patients using the 6 minute walk test (6MWT) and fatigue questionnaires as outcome measures. MMPOWER-3 was designed to provide important baseline characteristics and data on how treatment may impact functional changes and PROs.

METHODS

Study design and participants

MMPOWER-3 was a 24-week, randomized, double-blind, parallel-group, placebo-controlled clinical trial for adults with PMM conducted at 27 clinical research centers in 7 countries (Canada, Denmark, England, Germany, Hungary, Italy, and US).

MMPOWER-3 trial participants were primarily identified by the RePOWER registry, a global, prospective, non-interventional registryenrolling 413 ambulatory subjects 16-80 years of age with signs and/or symptoms of PMM [30]. Registry subjects provided demographic, genetic/phenotypic, functional, and clinical assessments, which were used to confirm genotypic-phenotypic correlations and identify potential phase 3 trial participants prior to MMPOWER-3 screening [30].

Following screening (7 to 28 days), eligible participants were randomized in a 1:1 ratio to receive either 24-weeks of once-daily SC dosing of 40mg elamipretide or placebo. Study drug or placebo were self-administered subcutaneously by trained participants or their caregivers, at rotating sites around four quadrants of the abdomen or the thighs. Treatment began at the baseline visit with assessments at Weeks 4, 12, and 24.

Eligible participants were ≥16 and ≤ 80 years of age (≥18 years in Germany), diagnosed with PMM with a confirmed mutation affecting mitochondrial function, and symptoms (i.e. exercise intolerance, fatigue, muscle weakness) and/or physical examination findings consistent with a myopathy as the predominant manifestations of their mitochondrial disease. In addition, participants had to be willing and able to provide consent and adhere to trial requirements for

inclusion. An acceptable form of birth control was required of participants of child-bearing potential during the study.

Participants walking <100 meters or >450 meters during the 6MWT at screening/baseline were also excluded. Participants were not allowed to have had a recent (within 30 days) or planned hospitalization/procedure and were excluded if they had a clinically significant end-organ damage in the opinion of the investigator [30].

Standard Protocol Approvals, Registrations, and Patient Consents

MMPOWER-3 was conducted in accordance with international ethics guidelines, including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, ICH GCP guidelines, and all applicable laws and regulations. The study was approved by institutional review boards, and all participants provided written informed consent. (clinicaltrials.gov, Clinical Trials Identifier: NCT03323749.)

Randomization and Masking

Assignment to treatment groups within each cohort for the randomized portion of the study was determined by a computer-generated random sequence using an Interactive Web-Response System to assign identical glass vials containing either the elamipretide or a placebo, which consisted of the same formulation without elamipretide. Participants were stratified by the subclassification of the specific mutation causing their PMM as determined by the adjudication committee formed to review and confirm eligibility for study enrollment [3]. The pharmacists, investigators and trial staff, sponsor, and participants were blinded to treatment.

Study Assessments and Procedures

MMPOWER-3 was designed to assess the safety and efficacy of elamipretide through primary and secondary clinical study endpoints.

Efficacy Assessments

Co-primary endpoints evaluated the effect of elamipretide for 24 weeks including the distance walked (in meters) on the 6MWT, and the Total Fatigue score on the Primary Mitochondrial Myopathy Symptom Assessment (PMMSA) previously described in detail [31]. The full PMMSA assesses the severity of 10 of the most common symptoms of PMM using the following 4-point scale (not at all [1] to severe [4]; described later). PMMSA Total Fatigue score (TFS) focuses on myopathic symptoms most commonly associated with PMM (severity of tiredness and muscle weakness at rest and during activities as described by participants).

Most Bothersome Symptom Score on the PMMSA as well as the NeuroQoL Short Form Fatigue scores were secondary endpoints. The Neuro-QoL evaluates and monitors sensations ranging from tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that decreases capacity for physical, functional, social, and mental activities, based on a 5-point scale (1=Never, 2=Rarely, 3=Sometimes, 4=Often, and 5=Always).

Other secondary endpoints included the Patient– and Clinician–Global Impression (PGI and CGI) of PMM Symptoms. PGI and CGI assess patient and clinician overall assessment of the severity of the patient's symptoms related to PMM on a 5-point scaled question scored 0 to 4 (0=None, 1=Mild, 2=Moderate, 3=Severe, 4=Very Severe) and changes to their symptoms on a

7-point scale scored -3 to 3 (-3=very much worse, -2=moderately worse, -1=a little worse, 0=no change, 1=a little better, 2=moderately better, 3=very much better).

The PMMSA was performed during screening, baseline, and daily throughout the 24-week study period. Other efficacy endpoints were performed at screening, baseline, and at Weeks 4, 12, and 24 of randomized treatment.

Safety Assessments

Safety and tolerability of elamipretide 40mg/d SC were assessed through recording of adverse events (AEs), ascertained via self-report, vital signs, physical exam, ECGs, and clinical laboratory evaluations. Adverse events were assessed for severity and relationship to study medication throughout the 24-week study. Safety measures were assessed during screening, baseline and weeks 4, 12, and 24.

Statistical Analysis

A sample size of 202 participants, with 101 participants in each treatment arm, was determined to provide 90% power to detect a 30-meter difference between treatment groups in the 6MWT and a 90% power to detect a one-unit difference in the PMMSA TFS. This was assuming standard deviations of 60 meters for 6MWT and 2 units for the PMMSA TFS, at an alpha-level of 0.025, as established from a previous study of elamipretide in patients with PMM [11]. The 2-sided alpha-level of 0.025 was used to account for a possible multiplicity adjustment for the primary efficacy endpoints.

Efficacy was assessed in the intention to treat (ITT) population, defined as all participants who received at least one dose of investigational medication, and the per-protocol (PP) population, which included all ITT participants without defined protocol violations/deviations identified per blinded data review prior to database lock. These protocol violations/deviations included not meeting inclusion/exclusion criteria or having a selected major protocol deviation deemed to potentially impact efficacy findings; not completing the study; not receiving investigational treatment within two days prior to the Week 24 visit; having <80% compliance to investigational product; and not completing the study. Safety was assessed in the safety population, defined as all participants who received at least one dose of investigational medication.

Primary and secondary efficacy outcomes were assessed as the change from baseline to each on-treatment time point with the primary time point being end of treatment (Week 24). Analyses of continuous endpoints were conducted utilizing a mixed model repeated measures approach, with fixed effects for treatment, visit, the treatment-by-visit interaction, and participant as a random effect. The baseline value and a baseline-by-visit interaction for the endpoint were included as covariates. A family-wise alpha level of 0.05 was maintained for the primary endpoints, using Hochberg's procedure at the primary time point of 24 weeks. If both primary endpoints were significantly different from placebo at the 0.05 (2-sided) level of significance in favor of elamipretide, then both endpoints were considered statistically significant. If not, the endpoint with the smaller *p*-value of the two was considered statistically significant if the *p*-value was ≤0.025 (2-sided).

In the event that both endpoints in the primary endpoint family were significant at the 5% level, then secondary endpoints were to be tested at Week-24 with Type I error control, achieved by

testing sequentially using a two-sided alpha level of 0.05. The endpoints and hierarchy of comparisons was: (1) change from baseline in Neuro-QoL Fatigue Short Form (T-score); (2) change from baseline in PGI of PMM Symptoms; (3) change from baseline in CGI of PMM Symptoms; (4) change from baseline in most bothersome symptom score on the PMMSA. Sequential comparisons to control Type I error were only to be completed if previous comparisons were statistically significant. For these analyses, *p*-values were nominal.

Subgroup Analyses by PMM Genotype

Given the extensive genetic heterogeneity of the study population, an exploratory analysis of genetic subgroups by genomic alteration (mtDNA and nDNA) was performed using the same methods as described for the primary efficacy endpoints above (ITT population using similar Mixed Model Repeated Measures [MMRM] models).

As a result of a potential data entry error, which was later identified in post hoc data analysis, three participants were mis-classified in the clinical study report as having a pathogenic mtDNA variant. Post-hoc analyses revealed that these three participants instead had nDNA mutations, either in *POLG* (two participants) or *TWNK* (in one subject). Accordingly, these participants were moved from the mtDNA group into the nDNA cohort for the included genetic mutation analyses. 6MWT for one subject at week 24 was deemed unusable because the participant inadvertently received walking assistance, and was therefore not included in the 6MWT analyses.

Study protocol and statistical analysis plan were published on ClinicalTrials.gov updated on January 24th 2022 (NCT03323749) [32].

Pharmacokinetic Analysis

The PK Population included 106 subjects randomized and treated with elamipretide, with at least one PK sample taken during their participation. PK modelling for elamipretide and its metabolites, M1 and M2, were performed using NONMEM computer software. Covariates, such as age, genotype, weight, height, lean body mass, body mass index, liver function tests, serum creatinine, and renal function (as described by estimated glomerular filtration rate [eGFR]) were analyzed. The exposure-response analysis examined response based on the 6MWT as a function of steady-state exposure to elamipretide and its metabolites.

Role of the funding source

The funding source for this study participated in the development of the study design. All authors participated in data collection, data interpretation, and the clinical study report writing. The manuscript lead author had full access to the totality of the study data. The remaining authors were provided with an aggregate data analysis. All authors had final responsibility for the decision to submit for publication.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Protocol and Statistical Analysis Plan

The study protocol and statistical analysis plan were published[32].

RESULTS

Participants

Of the 296 participants screened for eligibility in MMPOWER-3, 218 were enrolled and randomized to treatment (elamipretide n=109; placebo n=109) between October 2017 and December 2019 (**Figure 1**). Of thosereceiving investigational product (n=218), 205 (94%) completed the double-blind period of the study, with a similar percentage of participants for each treatment group completing (n=102 [93.6%] elamipretide and n=103 [94.5%] placebo). Thirteen randomized participants (6.0%) discontinued treatment (main reason being participant decision; n=9 [4.1%]). Most participants (90.8%; n=198/218) were included in the PP patient population (n=96 [88.1%] for elamipretide and n=102 [93.6%] for placebo).

Participant demographics at baseline were similar between treatment groups and characteristics demonstrated similar impairment in PMM (**Table 1**). Of the 218 treatment-randomized participants, the mean age was 44.9 years with participants mostly being white (94%; n=203/218) and female (64.2% n=140/218). Mean weight was 66.0 (±18.9) kg, height was 165.7 (±10.4) cm, and BMI was 24.0 (±6.0). Among the participants that completed the 6MWT at baseline, the average distance walked was 330.28 (±76.5) meters. One participant had a protocol violation of walking >450 meters on the 6MWT at baseline. The mean PMMSA TFS was 10.6 (±2.5). The Neuro-QoL Fatigue Short Form average T-score was 55.0 (±7.5) points. At screening, participants reported tiredness during activities (28.9%; n=63), muscle weakness during activities, (21.1%; n=46), balance problems (11.5%; n=25), and tiredness at rest (10.6%; n=23) on the PMMSA as the most bothersome symptom of the 10 symptoms of PMM, with bothersome symptoms varying slightly between treatment groups. (**Table 2**).

Baseline genetic test results showed a majority of participants (74%, n=162) had mtDNA mutations, with the remainder (26%, n=56) having nDNA defects (**Table 3 and eFigure 1**). Because participants were stratified by the subclassification of the genetic class, the distribution of genetic class between mtDNA and nDNA was similar between treatment groups. Three participants were mis-classified in the clinical study report (identified in a post-hoc analysis) as having a pathogenic mtDNA variant. Instead, these three participants had nDNA mutations (either in *POLG* [two participants] or *TWNK* [in one subject]). Accordingly, these participants were moved from the mtDNA group into the nDNA cohort for the genetic mutation analyses, resulting in 73% (n=159) with mtDNA mutations, and the remaining 27% (n=59) with nDNA defects.

Efficacy

Primary Endpoints of Overall ITT

Analysis of the 6MWT at the end of treatment showed the Least Squares (LS) Mean (SE) of change from baseline in distance walked at Week 24 was 14.1 (±5.7) meters for participants receiving elamipretide and 17.3 (±5.7) meters for participants receiving placebo, a –3.2 meter difference between the two groups (95% confidence interval [CI], –18.7, 12.3; p= 0.69) (**Figure 2A**). The per-protocol (PP) participant analysis demonstrated a –2.2 meter difference between the two groups (95% CI, –16.9, 12.5; p= 0.77).

Elamipretide-treated participants reported more total fatigue at baseline and less total fatigue at end-of-treatment as assessed by the PMMSA TFS. The LS Mean (SE) of change from baseline to Week 24 on the PMMSA TFS was –1.13 (±0.22) for participants receiving elamipretide and –1.05 (±0.22) for participants receiving placebo, a –0.07 difference between the two groups (95%

CI, –0.69, 0.54; *p*= 0.81) (**Figure 2B**). The PP participant analysis demonstrated a 0.09 difference between the two groups (95% CI, –0.54, 0.72; *p*= 0.78).

Secondary endpoint results are provided in **eTable 1**. Analyses of change from baseline in PGI of PMM Symptoms and CGI of PMM Symptoms at the end of treatment are provided in **Figures 2C and 2D**, respectively.

Analyses by Genetic Subgroup: mtDNA versus nDNA

mtDNA: Subgroup analysis for participants with mtDNA mutations of the 6MWT at the end-of-treatment showed the LS Mean (SE) of change from baseline in distance walked at Week 24 was 14.0 (±6.1) meters for participants receiving elamipretide (n=74) and 25.0 (±6.1) meters for participants receiving placebo (n=79), an –11.0 meter between-group difference favoring placebo (95% CI, –28.1, 6.1; *p*= 0.21; **Figure 3A**).

nDNA: For participants with nDNA mutations (post-hoc analysis), LS Mean (SE) change from baseline in distance walked at Week 24 was 25.5 (±8.0) for participants receiving elamipretide (n=29) and 0.3 (±7.7) meters for participants receiving placebo (n=29), a 25.2 meter difference between the two groups favoring elamipretide (95% CI, 3.1, 47.3; *p*= 0.03; **Figure 3B**).

For participants with mtDNA mutations, the LS Mean (SE) of change from baseline at Week 24 on the PMMSA TFS was –1.3 (±0.2424) for participants receiving elamipretide and –1.1 (±0.2525) for participants receiving placebo, a –0.21 difference between the two groups (95% CI, –0.9, 0.5; *p*= 0.55). For participants with nDNA mutations (post-hoc analysis), LS Mean (SE) of change from baseline at Week 24 was –0.45 (±0.25) for participants receiving elamipretide and –0.48 (±0.24) for participants receiving placebo, a 0.03 difference between the groups (*p*=0.93).

Safety

In total, 109 participants received elamipretide and 109 received placebo. AEs during the treatment period were reported by a higher percentage of elamipretide participants (98.2% [n=107/109]) than placebo (76.1% [n=83/109]) **(Table 4)**. Most AEs in the elamipretide group (97.2%) and half of AEs in the placebo group (51.4%) were reported as treatment-related AEs. Most AEs were mild or moderate in intensity. The most commonly reported AEs for participants receiving elamipretide (frequency >10%) were injection site reactions (see **Table 4**). Injection site reactions experienced with elamipretide included erythema, pruritus, pain, swelling, induration, bruising, hemorrhage, urticaria, and injection site nodules and masses. A low percentage of serious adverse events (SAEs) were reported for participants in the elamipretide (n=5/109 [4.6%]) and the placebo groups (n=3/109 [2.8%]) and were not deemed to be treatment related. The incidence of AEs leading to discontinuation was greater in the elamipretide group (n=8/109 [7.3%] and n=2/109 [1.8%] for placebo, respectively). No participants had an AE with an outcome of death or hospitalization.

Pharmacokinetics

Population pharmacokinetic models were fit successfully to three analytes, elamipretide and two metabolites, M1 and M2. For elamipretide, systemic parameters scaled allometrically. No covariates influenced the systemic or absorption parameters. For M1 and M2, apparent clearance decreased with age and increased with renal function. No other covariates influenced the systemic parameters. In the exposure-response analysis, subjects with an nDNA mutation had an increase in the change and fractional change at Week 24 compared to the Day 1 (i.e., baseline) value for the 6MWT as a function of the elamipretide steady state area under the curve (p=0.0262 and p=0.0345, respectively).

Classification of Evidence

This study provides Class I evidence that elamipretide does not improve the 6 minute walk test or fatigue at 24 weeks compared to placebo in patients with primary mitochondrial myopathy.

DISCUSSION

We present the results of the first Phase 3 trial in PMM with elamipretide. Overall, participants that received elamipretide did not meet either primary or secondary endpoints. Specifically, there were no statistically significant changes between elamipretide and placebo in the 6MWT or the PMMSA Total Fatigue Score. MMPOWER-3 uncovered several findings, specifically the importance of considering pathogenic genotypes within the PMM population when evaluating the effect of investigational treatments. Among the most interesting findings of the trial, identified in a post-hoc analysis, was that PMM participants with nDNA defects performed significantly better on the 6MWT, whereas participants with mtDNA mutations did not differ from placebo. The insight from these subgroups are novel findings and are expected to contribute substantially to future PMM studies.

Patient improvements in 6MWT and PMMSA Total Fatigue Scores from the current study showed a similar trend as those results obtained from the phase 1/2 (MMPOWER-1) and phase 2 (MMPOWER-2) clinical trials of elamipretide in patients with PMM [10,11]. MMPOWER-1 [10] informed the dose selection for the phase 2 and 3 studies while the results from the phase 2 study, MMPOWER-2 [11], provided an efficacy signal and data to support the initiation of this phase 3 study.

While the current study did not meet either of its primary endpoints (changes in the 6MWT and PMMSA Total Fatigue Score), participants treated with elamipretide did report slightly less total fatigue (between-group difference was not statistically significant) at the end-of-treatment as assessed by the PMMSA Total Fatigue Score. Future studies are needed to elucidate whether the slight change in PMMSA Total fatigue score in treated and untreated participants is within the test variability range or a true measure of fatigue improvement not reaching statistical significance due to the mild-to-moderate impairment of participants at baseline and increased heterogeneity in participant selection.

The response in 6MWT in the nDNA cohort, as a function of plasma Area under the Curve (AUC0-24) demonstrates a statistically significant correlation, which supports this subgroup finding and suggests that the therapeutic dose may not be optimized. It is possible that the exposure-response relationship may differ by genotype/phenotype. These findings warrant further investigation and clearly underscore the importance of considering genetic subtypes in mitochondrial myopathy and the drug mechanism of action. All of the genes responsible for mtDNA maintenance are expressed in the nuclear genome [33]. Mitochondrial proteins/enzymes that are synthesized from nDNA must be transported across the inner mitochondrial membrane, enriched with cardiolipin [34]. These metabolite and nucleotide transporters depend on cardiolipin for their assembly and activity [35,36], and cardiolipin is known to stabilize mtDNA packaging into nucleoids [37]. It is intriguing to speculate that elamipretide's benefit in the nDNA cohort was caused by improved enzyme/metabolite transport into mitochondria, improved assembly and morphology of mitochondria, augmented mtDNA stability, reductions in ROS, or any combination thereof. Although these presumptions are supported by pre-clinical work where

elamipretide improved mitochondrial protein import and mitochondrial morphology [13,27,38], further investigation will advance our understanding of the 6MWT increase in the nDNA cohort.

Although the patient population with PMM included in the MMPOWER-3 study was impaired on the 6MWT at baseline compared with literature-based healthy controls (655 [±91] meters) [33], the phase 3 population was only moderately impaired based on the average PMMSA fatigue score, and only slightly more impaired than the population norm on the Neuro-QoL Fatigue Short Form T-score (mean T-score ≥50 points at baseline). In these mildly to moderately impaired participants, elamipretide did not demonstrate statistically significant changes on the primary endpoints (6MWT and PMMSA TFS) from baseline to 24 weeks compared with placebo. Additional analyses involving functional and patient reported outcomes are necessary to assess the ability of elamipretide to affect positive changes in genetically defined subgroups of this patient population.

In this phase-3 study, elamipretide was generally well tolerated. Most AEs were mild to moderate in severity, with the most commonly reported AEs including injection site reactions. This safety was similar to that observed in the MMPOWER-2 study [11], and the TAZPOWER study in patients with Barth Syndrome with no serious AEs or deaths [12].

Lessons Learned

There are important lessons to be learned from the present clinical trial regarding trial design in PMD. The first is that a better understanding of the natural history of PMM will help in future studies. Although the RePOWER pretrial, non-interventional registry [30] did not facilitate the

ability to study effort-dependent endpoints, it did enhance the understanding of disease mechanisms and de-risk/homogenize disease group selection for trial participants according to the specific drug intended targets but not the effort dependent endpoints.

The second lesson is that there is a clear need to further study meaningful endpoints in this patient population. Fatigue has been identified as the primary issue from which this patient population suffers, identifying a definitive focal point to be addressed in future therapeutic trials. Refining the sensitivity of the PMMSA fatigue scores in PMD and PMM further to capture signals is tantamount for future studies to address data gaps.

The lack of available biomarkers for PMM also presented challenges. The variability of participants responses to the PMMSA-Total Fatigue score, which is susceptible to a placebo effect were all challenges that skewed the objectivity of the study endpoints. Further, the mild to moderate fatigue scores observed at baseline point to a lack of sensitivity of this endpoint. The identification of objective endpoints or biomarkers assessing PMM would be beneficial for future trial design since the availability of biomarkers helps to target subjects that are most likely to respond to treatment, providing the ability to verify target engagement which could allow the use of enrichment strategies and reduce reliance on effort-dependent endpoints. For example, altered plasma acylcarnitine levels have previously been seen in PMM patients [39]**,** and elamipretide has been shown to reduce plasma acylcarnitines in other PMD [40], but the relation of this biomarker to clinically meaningful changes in daily life needs to be established.

The third lesson is from the basket design from MMPOWER-3, which pooled both nDNA and mtDNA participants. The placebo effect on 6MWT was prominent in mtDNA participants in the pre-specified subgroup analysis, and given the size of this subgroup this drove the placebo effect observed in the trial. Conversely, there was not a discernable placebo response on 6MWT in

nDNA participants (depicted in **Figure 3B**) as identified in a post-hoc analysis. Based on these observations, it appears that the MMPOWER-3 basket trial design introduced insurmountable heterogeneity. It has been shown that substantial efficiencies are possible in basket trial design only if the investigational drug works in most or all baskets in the clinical study, with losses of power and statistical significance if the investigational drug only works in a single basket [41]. The basket trial design used in MMPOWER-3 introduced significant heterogeneity between participants with mtDNA and nDNA mutations, which was particularly apparent with 6MWT results seen in the pre-specified subgroup analysis by genetic abnormality. Therefore, it is doubtful that a separation in efficacy between active treatment and placebo would have been observed regardless of the length of the trial. This critical lesson advances our understanding of the various PMM genotypes, and highlights the need to critically consider particular genotypes in the design of future trials.

CONCLUSIONS

The MMPOWER clinical development program was the most advanced and complete in PMM and provided significant lessons regarding study design and patient enrollment parameters. MMPOWER-3 was the first trial that progressed into phase 3 to assess a therapy for participants with PMM. Although the primary endpoints were not met for the overall population, the observation of the improvement in the 6MWT in the nDNA subgroup is encouraging and hypothesis generating. Efforts are currently underway to confirm this positive benefit and these findings in a follow-up and targeted phase 3 trial in PMM participants with pathogenic nDNA variants.

WNL-2023-000248_efig1 --- http://links.lww.com/WNL/C851

WNL-2023-000248_etab1 --- http://links.lww.com/WNL/C852

REFERENCES

1. Mancuso M, Hirano M. NORD Physician Guide to Mitochondrial Myopathies (MM). *Nat Org Rare Disord*. 2016:1–8.
2. Mancuso M, McFarland R, Klopstock T, Hirano M. International workshop: outcome measures and clinical trial readiness in primary mitochondrial myopathies in children and adults. *Neuromuscul Disord*. 2017:1–12.
3. Rahman J, Rahman S. Mitochondrial medicine in the omics era. Lancet. 2018 Jun 23;391(10139):2560-2574.
4. Pfeffer G, Chinnery P. Diagnosis and treatment of mitochondria myopathies. *Ann Med.* 2013;45:4–16.
5. Tarnopolsky M. Exercise testing as a diagnostic entity in mitochondrial myopathies. *Mitochondrion.* 2004;4:529–42.
6. Gorman GS, Schaefer AM, Ng Y, Gomez N, Blakely EL, Alston CL, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. *Ann Neurol.* 2015;77(5):753-9.
7. Genge A, Massie R, Shefner J, Dashe J. Mitochondrial myopathies: Clinical features and diagnosis. UpToDate® (Wolters Kluwer) 2013.
8. Ahmed S, Craven L, Russell OM, Turnbull DM, Vincent AE. Diagnosis and treatment of mitochondrial myopathies. *Neurotherapeutics*. 2018;15(4):943–53.
9. Szeto HH, Birk AV. Serendipity and the discovery of novel compounds that restore mitochondrial plasticity. *Clin Pharmacol Ther*. 2014;96:672-683.
10. Karaa A, Haas R, Goldstein A, Vockley J, Weaver WD, Cohen BH. Randomized dose-escalation trial of elamipretide in adults with primary mitochondrial myopathy. *Neurology*. 2018;90(14):e1212–e1221.
11. Karaa A, Haas R, Goldstein A, et al. A randomized crossover trial of elamipretide in adults with primary mitochondrial myopathy. *J Cachexia Sarcopenia Muscle.* 2020 Aug;11(4):909-918.
12. Thompson RW, Hornby B, Manuel R, Bradley E, Laux J, Carr J, Vernon HJ. A phase 2/3 randomized clinical trial followed by an open-label extension to evaluate the effectiveness of elamipretide in Barth syndrome, a genetic disorder of mitochondrial cardiolipin metabolism. *Genet Med*. 2021 Mar;23(3):471-478.
13. Sabbah HN, Gupta RC, Singh-Gupta V, Zhang K. Effects of elamipretide on skeletal muscle in dogs with experimentally induced heart failure. *ESC Heart Failure*. 2019;6:328-335.
14. Xu Y, Malhotra A, Ren M, Schlame M. The enzymatic function of tafazzin. *J Biol Chem.* 2006;281:39217–24.
15. Grazioli S, Pugin J. Mitochondrial Damage-associated molecular patterns: from inflammatory signaling to human diseases. *Front Immunol.* 2018;9:832.
16. Birk A, Liu S, Soong Y, et al. The mitochondrial-targeted compound SS-31 reenergizes ischemic mitochondria by interacting with cardiolipin. *J Am Soc Nephrol.* 2013;24:1250–61.
17. Birk AV, Chao WM, Bracken C, Warren JD, Szeto HH. Targeting mitochondrial cardiolipin and the cytochrome c/cardiolipin complex to promote electron transport and optimize mitochondrial ATP synthesis. *Br J Pharmacol.* 2014;171(8):2017–28.
18. Brown DA, Hale SL, Baines CP, et al. Reduction of early reperfusion injury with the mitochondria-targeting peptide Bendavia. *J Cardiovasc Pharmacol.* 2014;19:121-32.

19. Eirin A, Ebrahimi B, Zhang X, Zhu X-Y, Woollard JR, He Q, Textor SC, Lerman A, Lerman LO. Mitochondrial protection restores renal function in swine atherosclerotic renovascular disease. *Cardiovasc Res*.2014;103(4):461–72.
20. Nickel A, Kohlhaas M, Maack C. Mitochondrial reactive oxygen species production and elimination. *J Mol Cell Cardiol*. 2014;73:1–8.
21. Baback Roshanravan, Sophia Z. Liu, Eric G. Shankland, John K. Amory, H. Thomas Robertson, View ORCID Profile. David J. Marcinek, Kevin E. Conley. In Vivo Mitochondrial ATP Production Is Improved in Older Adult Skeletal Muscle After a Single Dose of Elamipretide in a Randomized Trial. *MedRxiv*. 2021. doi: https://doi.org/10.1101/2020.09.30.20200493
22. Siegel M, Kruse S, Percival J, et al. Mitochondrial-targeted peptide rapidly improves mitochondrial energetic and skeletal muscle performance in aged mice. *Aging Cell.* 2013;12:763-771.
23. Stauffer B, Sparagna G, Chau S, et al. MTP131, a cardiolipin targeting peptide, improves mitochondrial activity in the failing human heart. *Eur J Heart Fail Abstr Suppl* 2016;18:289.
24. Szeto HH, Liu S, Soong Y, et al. Mitochondria-targeted peptide accelerates ATP recovery and reduces ischemic kidney injury. *J Am Soc Nephrol.* 2011;22: 1041-52.
25. Szeto HH, Schiller PW. Novel therapies targeting inner mitochondrial membrane--from discovery to clinical development. *Pharm Res.* 2011;28(11):2669-79.
26. Zhao K, Luo G, Giannelli S, Szeto HH. Mitochondria-targeted peptide prevents mitochondrial depolarization and apoptosis induced by tert-butyl hydroperoxide in neuronal cell lines. *Biochem Pharmacol*. 2005;70(12):1796-1806.
27. Allen ME, Pennington ER, Perry JB, et al. Mitochondrial cristae networks in the post-ischemic heart: mitigation of ultrastructural and functional derangements with a cardiolipin-binding peptide. *Nature Communications Biology*. 2020;3(389).
28. Chatfield KC, Sparagna GC, Chau S, Phillips EK, Ambardekar AV, Aftab M, Mitchell MB, Sucharov CC, Miyamoto SD, Stauffer BL. Elamipretide Improves Mitochondrial Function in the Failing Human Heart. *JACC Basic Transl Sci*. 2019 Apr 29;4(2):147-157.
29. Vincent AE, Ng YS, White K, Davey T, Mannella C, Falkous G, Feeney C, Schaefer AM, McFarland R, Gorman GS, Taylor RW, Turnbull DM, Picard M. The Spectrum of Mitochondrial Ultrastructural Defects in Mitochondrial Myopathy. *Sci Rep*. 2016 Aug 10;6:30610.
30. An Observational Study of Patients With Primary Mitochondrial Disease (SPIMM-300) (RePOWER). Available at: https://clinicaltrials.gov/ct2/show/NCT03048617?term=repower&draw=2&rank=1. Accessed June 7, 2021.
31. Gwaltney C, Stokes J, Aiudi A, Mazar I, Ollis S, Love E, Espensen A, Shields AL. Development of a Patient-Reported Outcome Questionnaire to Evaluate Primary Mitochondrial Myopathy Symptoms: The Primary Mitochondrial Myopathy Symptom Assessment. *J Clin Neuromuscul Dis*. 2020 Dec;22(2):65-76.
32. A Trial to Evaluate Safety and Efficacy of Elamipretide Primary Mitochondrial Myopathy Followed by Open-Label Extension (MMPOWER-3): Available at https://clinicaltrials.gov/ct2/show/NCT03323749?term=elamipretide&draw=2&rank=9
33. El-Hattab AW, Craigen WJ, Scaglia F. Mitochondrial DNA maintenance defects. *Biochim Biophys Acta Mol Basis Dis*. 2017 Jun;1863(6):1539-1555.

34. Brown DA, Sabbah HN, Shaikh SR. Mitochondrial inner membrane lipids and proteins as targets for decreasing cardiac ischemia/reperfusion injury. *Pharmacol Ther*. 2013 Dec;140(3):258-66.
35. Gebert N, Joshi AS, Kutik S, Becker T, McKenzie M, Guan XL, Mooga VP, Stroud DA, Kulkarni G, Wenk MR, Rehling P, Meisinger C, Ryan MT, Wiedemann N, Greenberg ML, Pfanner N. Mitochondrial cardiolipin involved in outer-membrane protein biogenesis: implications for Barth syndrome. *Curr Biol*. 2009 Dec 29;19(24):2133-9.
36. Chicco AJ, Sparagna GC. Role of cardiolipin alterations in mitochondrial dysfunction and disease. *Am J Physiol Cell Physiol*. 2007 Jan;292(1):C33-44.
37. Luévano-Martínez LA, Forni MF, dos Santos VT, Souza-Pinto NC, Kowaltowski AJ. Cardiolipin is a key determinant for mtDNA stability and segregation during mitochondrial stress. *Biochim Biophys Acta*. 2015 Jun-Jul;1847(6-7):587-98.
38. Zhao H, Li H, Hao S, Chen J, Wu J, Song C, Zhang M, Qiao T, Li K. Peptide SS-31 upregulates frataxin expression and improves the quality of mitochondria: implications in the treatment of Friedreich ataxia. *Sci Rep*. 2017;7(1):9840.
39. Vissing CR, Dunø M, Wibrand F, Christensen M, Vissing J. Hydroxylated Long-Chain Acylcarnitines are Biomarkers of Mitochondrial Myopathy. *J Clin Endocrinol Metab*. 2019 Dec 1;104(12):5968-5976.
40. Oates PJ, Brown DA, Vernon HJ, Gangoiti JA, Barshop BA. Metabolomic biomarkers from patients with Barth syndrome treated with elamipretide: insights from the TAZPOWER study medRxiv 2020.11.20.20235580; doi: https://doi.org/10.1101/2020.11.20.20235580.
41. Cunanan KM, Iasonos A, Shen R, et al. An efficient basket trial design. *Stat Med.* 2017;36(10):1568-1579.

Tables

Table 1: Baseline Participants Demographics

	Elamipretide (n=109)	Placebo (n=109)
Age (years) Mean (SD) Median Range	45.5 (15.7) 47 16–75	44.3 (14.3) 46 16–74
Women, n (%)	67 (61.5)	73 (67.0)
Race (n [%])		
White	103 (94.5)	100 (91.7)
Black/Africa American	1 (0.9)	0
Asian	2 (1.8)	5 (4.6)
American Indian/Alaska Native	1 (0.9)	0
Other/Multiple	2 (1.8)	4 (3.7)
Weight (kg) Mean (SD) Median Range	64.8 (20.3) 62.5 29.7–181.4	67.2 (17.3) 64.2 31.4–123.3
Height (cm) Mean (SD) Median Range	165.6 (10.7) 165.0 123.0–197.3	165.7 (10.2) 165.0 137.5–192.8
BMI (kg/m2) Mean (SD) Median Range	23.5 (6.1) 22.2 12.4–48.9	24.4 (5.8) 23.2 11.7–45.9
Distance in 6MWT (meters)[a] Mean (SD) Median Range	324.95 (79.1) 343.33 (112.07–480.00)	335.65 (73.8) 351.00 (140.88–449.60)
Total Fatigue Score in PMMSA[b]	10.6 (2.5)	10.5 (2.5)

Mean (SD) Median Range	10.3 4–16	10.3 5–16
Neuro-QoL Fatigue – Short Form (Total T-Scores) Mean (SD) Median Range	55.0 (7.5) 55.4 36.5–74.1	54.4 (7.5) 56.6 38.2–74.1
PGI in PMM Symptoms Mean (SD) Median Range	2.1 (0.8) 2 0–4	2.0 (0.8) 2 0–4
CGI in PMM Symptoms Mean (SD) Median Range	1.9 (0.8) 2 0–4	1.9 (0.8) 2 0–4
Most Bothersome Symptom Score in PMMSA[b] Mean (SD) Median Range	2.99 (0.69) 3.0 1.0–4.0	2.84 (0.69) 3.0 1.1–4.0

[a]n=108 for placebo group.

[b]n=107 for placebo group.

6MWT=Six-minute Walk Test; BMI=body mass index; CGI=Clinician Global Impression; PGI=Patient Global Impression; PMM=primary mitochondrial myopathy; PMMSA=Primary Mitochondrial Myopathy Symptoms Assessment.

Table 2: Most Bothersome Symptom in PMMSA at Screening

	Elamipretide (n=109) n (%)	**Placebo (n=109)** n (%)
Tiredness at Rest	9 (8.3%)	14 (12.8%)
Tiredness during Activities	37 (33.9%)	26 (23.9%)
Muscle Weakness at Rest	4 (3.7%)	5 (4.6%)
Muscle Weakness during Activities	24 (22.0%)	22 (20.2%)
Balance Problems	11 (10.1%)	14 (12.8%)
Vision Problems	10 (9.2%)	7 (6.4%)
Abdominal Discomfort	5 (4.6%)	2 (1.8%)
Muscle Pain	7 (6.4%)	9 (8.3%)
Numbness	1 (0.9%)	2 (1.8%)
Headache	1 (0.9%)	8 (7.3%)

PMMSA=Primary Mitochondrial Myopathy Symptoms Assessment

Table 3: Participants' Genetic Classifications

	Elamipretide (n=109) n (%)	**Placebo (n=109) n (%)**	**All participants (N=218) n (%)**
mtDNA mutation	79 (72.5)	80 (73.4)	159 (72.9)
Impaired mitochondrial protein synthesis *in toto*	79 (72.5)	79 (72.5)	158 (72.5)
Affect the subunits of the respiratory chain	0	1 (0.9)	1 (0.5)
nDNA mutation	30 (27.5)	29 (26.6)	59 (27.1)
Genes encoding subunits or ancillary proteins of the respiratory chain	3 (2.7)	4 (0.7)	7 (3.2)
Defects of mtDNA maintenance	27 (24.8)	25 (22.9)	52 (23.9)

mtDNA=mitochondrial DNA; nDNA=nuclear DNA.

Table 4: Adverse Events for Participants in the Elamipretide and Placebo Groups

	Elamipretide (n=109) n (%)	Placebo (n=109) n (%)
AE Category		
Any AE	107 (98.2)	83 (76.1)
Any treatment-related AE	106 (97.2)	56 (51.4)
Any SAE*	5 (4.6)	3 (2.8)
Any treatment-related SAE	0	0
Any AE leading to treatment discontinuation	8 (7.3)	2 (1.8)
Any AE leading to treatment interruption	13 (11.9)	5 (4.6)
Death	0	0
AEs Reported by ≥5% of Participants in Either Treatment Group		
Injection site erythema	94 (86.2)	31 (28.4)
Injection site pruritus	82 (75.2)	10 (9.2)
Injection site pain	43 (39.4)	20 (18.3)
Injection site swelling	42 (38.5)	7 (6.4)
Injection site induration	31 (28.4)	6 (5.5)
Injection site urticaria	14 (12.8)	0
Injection site nodule	11 (10.1)	2 (1.8)
Injection site bruising	9 (8.3)	18 (16.5)
Injection site mass	9 (8.3)	2 (1.8)
Injection site hemorrhage	7 (6.4)	10 (9.2)
Injection site hematoma	0	7 (6.4)
Headache	8 (7.3)	4 (3.7)
Nasopharyngitis	8 (7.3)	2 (1.8)
Eosinophil count increased	7 (6.4)	0
Upper respiratory tract infection	7 (6.4)	7 (6.4)
Dizziness	6 (5.5)	3 (2.8)
Fall	6 (5.5)	3 (2.8)

Nausea	5 (4.6)	8 (7.3)
Diarrhea	3 (2.8)	9 (8.3)

*The only -treatment-related AEs leading to discontinuation were injection site related.

AE=adverse event; SAE=serious adverse event.

Figures

Figure 1: Participants Disposition

296 participants were screened, and 218 participants were randomized to treatment. Two (2) participants in the elamipretide group and 1 patient in the placebo group had the treatment withdrawn due to adverse event prior to the study discontinuation. The ITT population included 109 participants in the elamipretide group and 109 participants in the placebo group. The PP population included 102 participants in the elamipretide group and 103 participants in the placebo group. ITT=intention to treat; PP = per-protocol.

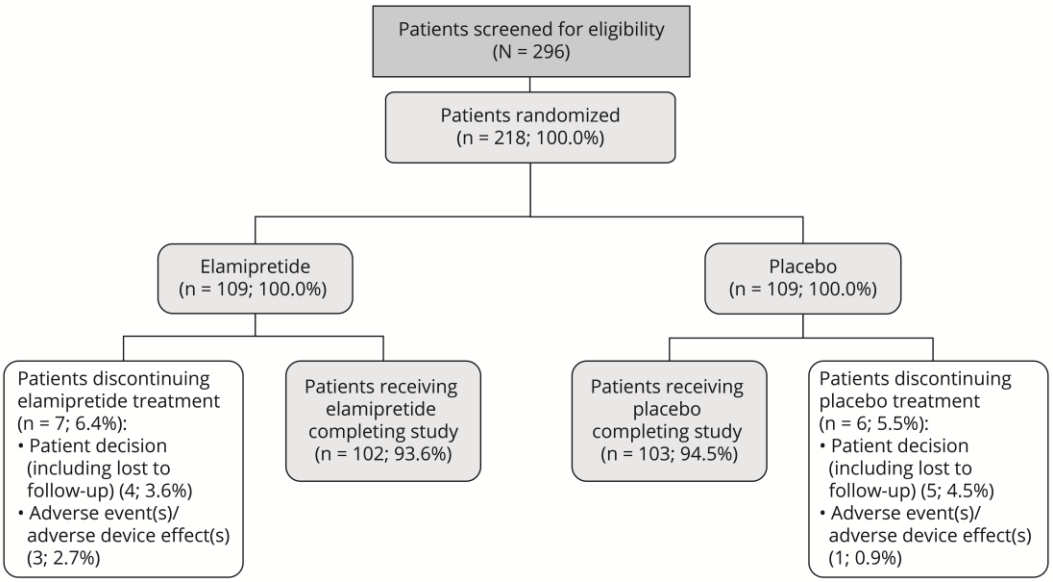


Figure 2: Endpoint Change from Baseline to End-of-Treatment (Week 24) in: Six-minute Walk Test (6MWT) (A), in Primary Mitochondrial Myopathy Symptom Assessment Total Fatigue Score (PMMSA) (B), in Patient Global Impression of Primary Mitochondrial Myopathy Symptoms (PGI) (C), and in Clinician–Global Impression of Primary Mitochondrial Myopathy Symptoms **(**CGI)

[a]No baseline measurements for two participants in the placebo group.

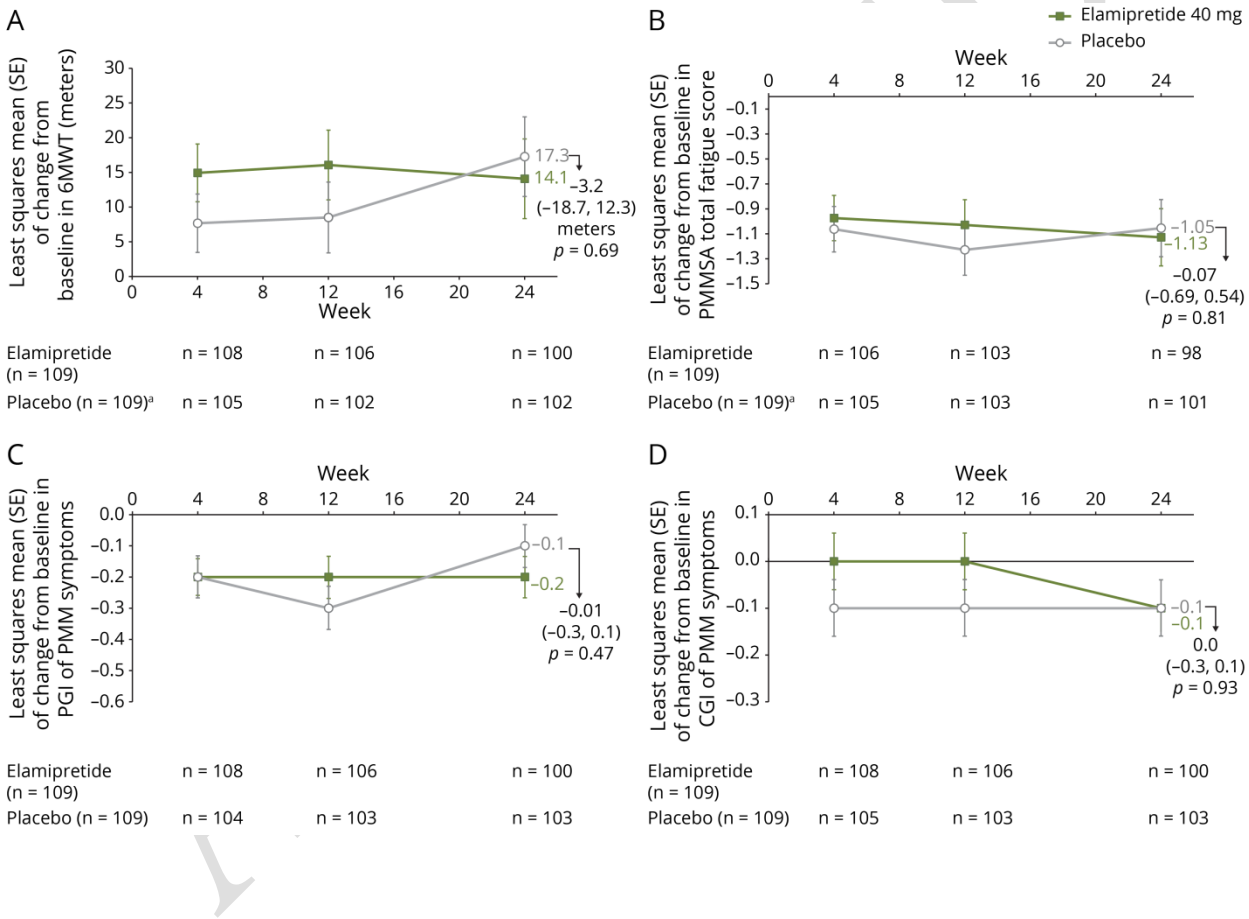
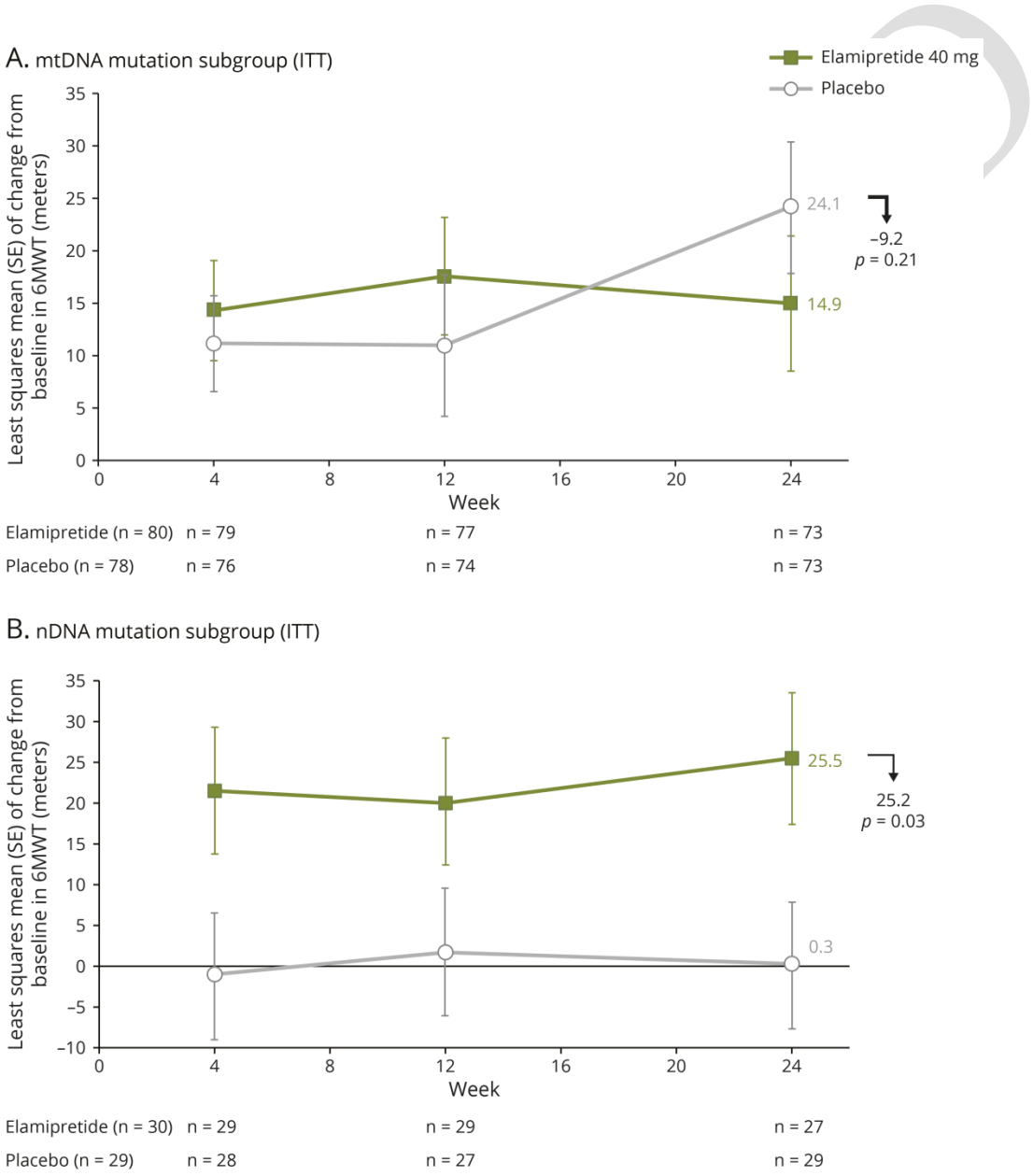


Figure 3: Change from Baseline to End-of-Treatment (Week 24) in Six-minute Walk Test: Subgroup Analysis by Genetic Abnormality

Subgroup analysis by genetic abnormality for change from baseline to end-of-treatment (Week 24) in 6MWT for (A) participants with mtDNA mutation and (B) participants with nDNA mutation



Efficacy and Safety of Elamipretide in Individuals With Primary Mitochondrial Myopathy: The MMPOWER-3 Randomized Clinical Trial

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