Elamipretide Improves Skeletal Muscle Function in Elderly Subjects: Results from a Randomized, Double-Blind, Placebo-Controlled, Single IV-Dose Study

Authors: Conley KE, PhD,1 Liu Z, PhD,1 Ali AS,1 Amory JK, MD,1 Robertson HL, MD,1 Goss C,1 Shankland EG, PhD,1 Marcinek DM, PhD,1 and Roshanravan B, MD1

1Department of Radiology, University of Washington Medical Center, Seattle, WA 98195, USA

ABSTRACT

Introduction: Mitochondrial dysfunction leads to reduced supply of ATP and may lead to overproduction of toxic levels of intracellular reactive oxygen species (ROS). Excess ROS results in oxidative damage to mitochondrial inner membranes and to cardiomyocytes, which stabilize the inner membranes. Oxidative damage can also cause sarcopenia and exercise intolerance. Mitochondrial dysfunction has been documented in heart failure (HF) patients, and exercise intolerance is a hallmark of the disease. Currently available treatments have not demonstrated the ability to improve skeletal muscle function in HF patients. The results of this trial, therefore, may have direct clinical implications for HF patients.

Hypothesis: Elamipretide (formerly referred to as Berapil, SS-31 and MTP-131 [ELAM]) is a mitochondria-targeting peptide that readily penetrates cell membranes and buiten mitochondrial membranes to locate on the inner membrane of mitochondria, where it associates with cardiolipin. In doing so, it improves the integrity and efficiency of the electron transport chain (ETC), thereby improving ATP synthesis and reducing the production of ROS. ELAM effectively improved muscle function and biomarker levels in multiple animal models of dysfunctions (specifically, age-related skeletal muscle immunodeficiency and chronic acidotic skeletal muscle dysfunction). We studied the effect of ELAM on skeletal muscle energetics and performance in elderly subjects.

Methods: Elderly subjects (≥60 and ≤85 yrs) with documented mitochondrial dysfunction and O2 demand, and improvement in sustained exercise performance in the muscle of elderly subjects.

Conclusions: ELAM may potentially target the mitochondrial dysfunction that exists in patients with HF, thereby improving sarcopenia and exercise tolerance. A statistical analysis of the results allowed for a comparison to previous studies in elderly patients that demonstrated a similar 36% increase in ATPmax post-6 months of endurance training.

INTRODUCTION

• Heart failure patients are frequently elderly with poor quality of life, exercise intolerance, fatigue, and muscle atrophy.

• Given the high energy demands of skeletal muscle, heart, and kidney, mitochondrial dysfunction is postulated to be a contributing factor.

• Six months of endurance training has been shown to improve bioenergetics in the elderly, but no approved therapies have demonstrated efficacy.

INTRODUCTION (cont.)

• Interventions

• Elamipretide selectively associates with cardiolipin, stabilizing ETC supercomplexes and mitochondrial cristae, which are essential for mitochondrial bioenergetics. ELAM improves ATP production and exercise function in mice.1,2

• ELAM improves mitochondrial function by increasing ATP production after a single infusion in a range of preclinical models.12

• Change from baseline in ATPmax with ELAM versus placebo 2 hrs post-infusion and after 7 days.

Efficacy assessments:

• 31P MRS

• Energetic state

• Muscle force-time-integral

• Fatigue test (force-time integral)

• Randomization

• Subjects were randomized to receive ELAM or placebo IV infusion.

• The treatment-emergent adverse events (TEAEs) were summarized as serious adverse events (SAEs) and adverse events (AEs) throughout the duration of the study.

• Subjects were excluded from the study if they were hospitalized within three months prior to screening.

• Selected Inclusion Criteria

• Elderly subjects (≥60 yrs of age and ≥85 yrs of age), with a body mass index (BMI) between 16 and 35kg/m^2 and a baseline 36% reduction in mitochondrial function (n = 38)

• Subjects were excluded from the study if they were hospitalized within three months prior to screening for a major medical condition, had uncontrolled hypertension, or symptoms of peripheral neuropathy.

• Safety Assessments

• Treatment-emergent adverse events (TEAEs) were summarized as SAEs and AEs throughout the duration of the study.

Energized Mitochondrial Membrane

Figure 1. Age-related changes in muscle physiology and the relationship between mitochondrial efficiency, aerobic capacity, and walking speed in elderly subjects.

Clinical Manifestations of Mitochondrial Dysfunction in the Elderly

Clinical manifestations of mitochondrial dysfunction in the elderly include alterations in whole body aerobic capacity, reduced muscle mitochondrial capacity, decreased muscle mitochondrial efficiency, and worsening mobility and quality of life.

STUDY OBJECTIVES

A Phase 2 randomized, double-blind, placebo-controlled study sought to evaluate the ability of a single intravenous dose of ELAM to improve skeletal muscle function in elderly subjects.

Primary

• Evaluate the effect of ELAM, given as an intravenous (IV) infusion, on whole body aerobic capacity (VO2 peak), muscle force-time-integral, and muscle fatigue test in elderly subjects with evidence of skeletal muscle mitochondrial dysfunction.

Secondary

• Evaluate the safety and tolerability of a single IV infusion of ELAM in elderly subjects with evidence of skeletal muscle mitochondrial dysfunction.

METHODS

Methods: Elderly subjects (≥60 and ≤85 yrs) with documented mitochondrial dysfunction received a single IV dose of ELAM 0.25 mg/(kg • hr), or placebo, infused at 60 mL/hr for 2 hrs, followed by 60 mL/hr for 2 hrs.

Results: ELAM treatment was evaluated for mitochondrial improvements on infusion day (Visit 2: change from baseline for ATPmax, and 7 days after infusion (Visit 4): P/O, O2 uptake, and ATPmax). Exercise tolerance was also evaluated 2 hrs after infusion (day 2) and on day 7.

Conclusions: ELAM treatment, in a single infusion, was evaluated for its potential to reverse mitochondrial dysfunction, and O2 demand, and improved sustained exercise performance in elderly subjects.

RESULTS

Figure 2. Beneficial effects of ELAM on mitochondrial function.11

Figure 3. ELAM improves ATP production and exercise function in mice.12

Figure 4. Measuring change in muscle performance.

Figure 5. Trial Design.6

Figure 6. Change from baseline in ATPmax with ELAM versus placebo 2 hrs post-infusion and after 7 days.

Figure 7. Observed increases in ATPmax with ELAM. Comparison to findings from a previous study of elderly patients after 6 months of endurance training.13

REFERENCES


Acknowledgements:

This study was supported by Shire BioSurgery. Medical writing assistance was provided by James A. Stoller, MPH, PhD, Lora K. Dettwyler, PhD, and Jennifer McKinley, MA.