Insights from the Clinical Development of Elamipretide for Primary Mitochondrial Disorders

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Leading Mitochondrial Medicine

Mitochondrial dysfunction as a new frontier

Our lead product candidate, elamipretide, targets cardiolipin, a phospholipid responsible for normal inner mitochondrial membrane structure and function.

- Observed improvement of mitochondrial function across multiple disease models
- No utilizable biomarkers identified – respiration assays and P31 NMR spectroscopy show improvements, but not operationalizable in multi-center clinical trials outside of academic settings
- Improves mitochondrial morphology, but PK/PD disconnect with therapeutic effects persisting beyond known half-life of molecule.
- Associates but does not bind covalently with cardiolipin, an anomaly in the traditional drug development landscape.
- Mitochondrial biology, and the critical role of cardiolipin in that biology, remains an evolving frontier.

We are evaluating elamipretide in Barth syndrome, primary mitochondrial myopathy, and Leber's hereditary optic neuropathy.

Barth Syndrome

Ultra-rare disease affecting <150 in the US. Caused by a genetic defect resulting in severe cardiolipin deficiency; diagnosed by the ratio of abnormal to normal cardiolipin. Characterized by fatigue, myopathy, cardiomyopathy, neutropenia. Life limiting (~85% mortality by age 5, overall reduced life-span). Advocacy and external expert appealed for clinical trial.

- Comprehensive natural history data is invaluable
  - Collected longitudinally between 2012 and 2019 by the same Johns Hopkins multi-disciplinary team that conducted our trial
  - Publications informed choice of functional endpoints for the clinical trial
  - Benchmark for open-label extension data
- Collaboration with the Barth Syndrome Foundation
  - Patient-Focused Drug Development Initiative
  - Extremely helpful for concept elicitation work for the PRO development
  - Scientific support from the Scientific and Medical Advisory Board

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Barth Syndrome Program: Key Insights

- Very small population (<150 in US) required creative study design considerations
  - 12 patients, double-blind placebo-controlled crossover design with prespecified efficacy assessments in ongoing open-label extension
- Phase 2 data suggests that longer treatment duration seems necessary
- Pre-specified subgroup analysis reveals differential (more rapid) response in efficacy predicted by baseline diagnostic biomarker values – aligns with mechanism of therapeutic agent
- Despite developing a PRO, the main protocol specified endpoints did not capture important breakthroughs/milestones for patients which were captured in a separate pre-specified video patient perception of change protocol and the clinical study notes
  - Amelioration of nighttime enuresis in teenagers
  - Newfound ability to participate in physical education at school
  - Mechanized cart at Boy Scout camp no longer required
  - Many examples of newfound appetite (low BMI is common in Barth, particularly during puberty)

Baseline MLCL/CL ratio predicted response

Assessment	Low ratio subjects (n=6)	High ratio subjects (n=6)	Between sub-group analyses using raw end-of-treatment period values
MLCL:CL screening ratio	*9.4*	*26.9*	
Δ 6MWT	42.6	-51.1	p=0.02
Δ BTHS-SA Total Fatigue	-0.45	0.41	p=0.47
Δ Clinician global impression of symptoms	-0.63	0.38	p=0.01
Δ Patient global impression of severity	-0.60	0.07	p=0.11
Δ PROMIS^ Fatigue	-1.60	2.40	p=0.45
Δ SWAY Balance	17.62	-1.58	p=0.11
Δ Muscle strength	-0.67	3.94	p=0.61
Δ 5X sit-to-stand	0.36	-0.10	p=0.77

Denotes improvement relative to placebo

^Patient Reported Outcomes Measurement Information System

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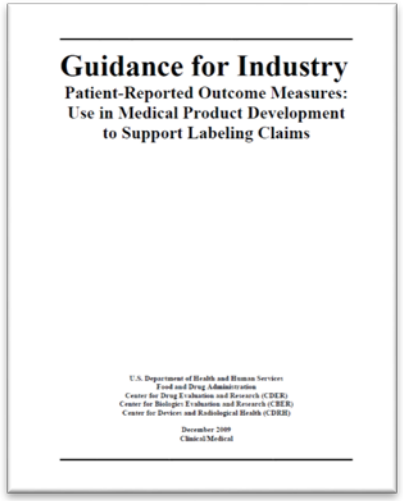
BarTH Syndrome Symptom Assessment (BTHS-SA)

Novel Endpoint Development Incorporating the Patient Voice



Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

BarTH Syndrome Symptom Assessment (BTHS-SA) – Adolescent version

Instructions: The following questions ask about **Barth Syndrome**. Please select the response that best describes your experience with Barth Syndrome **over the past 24 hours.** Please select only one answer for each question. Please answer all of the questions and do not skip any. There are no right or wrong answers to any of the questions.

Please indicate (with a check mark ☑) responses to the questions below.

1. Please rate your worst feeling of tiredness at rest in the past 24 hours.	No tiredness at all ☐	Mild tiredness ☐	Moderate tiredness ☐	Severe tiredness ☐	Very severe tiredness ☐
2. Please rate your worst feeling of tiredness during activities in the past 24 hours.	No tiredness at all ☐	Mild tiredness ☐	Moderate tiredness ☐	Severe tiredness ☐	Very severe tiredness ☐
3. Please rate your worst feeling of muscle weakness at rest in the past 24 hours.	No muscle weakness at all ☐	Mild muscle weakness ☐	Moderate muscle weakness ☐	Severe muscle weakness ☐	Very severe muscle weakness ☐
4. Please rate your worst feeling of muscle weakness during activities in the past 24 hours.	No muscle weakness at all ☐	Mild muscle weakness ☐	Moderate muscle weakness ☐	Severe muscle weakness ☐	Very severe muscle weakness ☐
5. Please rate your worst feeling of muscle pain at rest in the past 24 hours.	No muscle pain at all ☐	Mild muscle pain ☐	Moderate muscle pain ☐	Severe muscle pain ☐	Very severe muscle pain ☐
6. Please rate your worst feeling of muscle pain due to activities in the past 24 hours.	No muscle pain at all ☐	Mild muscle pain ☐	Moderate muscle pain ☐	Severe muscle pain ☐	Very severe muscle pain ☐
7. Please rate your worst feeling of early fullness when eating in the past 24 hours.	No feeling of early fullness at all ☐	Mild feeling of early fullness ☐	Moderate feeling of early fullness ☐	Severe feeling of early fullness ☐	Very severe feeling of early fullness ☐
8. Please rate your worst difficulty eating (for example, chewing and/or swallowing) in the past 24 hours.	No difficulty eating at all ☐	Mild difficulty eating ☐	Moderate difficulty eating ☐	Severe difficulty eating ☐	Very severe difficulty eating ☐
9. Please rate your worst feeling of headache in the past 24 hours.	No headache at all ☐	Mild headache ☐	Moderate headache ☐	Severe headache ☐	Very severe headache ☐

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PRO Concept Elucidation Aligned with Voice of Patient Report

EXPLORING THE SIGN AND SYMPTOM EXPERIENCE OF BARTH SYNDROME IN ADULT AND ADOLESCENT POPULATIONS

Authors: Jonathan Stokes,[1] Anthony Aiudi,[2] Iyar Mazar,[1] Meaghan Elliott,[2] Sarah Dillard,[1] Sarah Ollis,[1] Emily Love,[1] Alan L Shields,[1] Chad Gwaltney,[3]
[1]Adelphi Values, Boston, MA USA; [2]Stealth BioTherapeutics, Newton, MA USA; [3]Gwaltney Consulting Group, Westerly, RI USA

Table 3. Adult-reported Signs and Symptoms of BTHS (n=15)*

Cardiovascular signs and symptoms
- Cardiomyopathy (n=13, 86.7%)
- Arrhythmia (n=8, 53.3%)
- Low blood pressure (n=4, 26.6%)

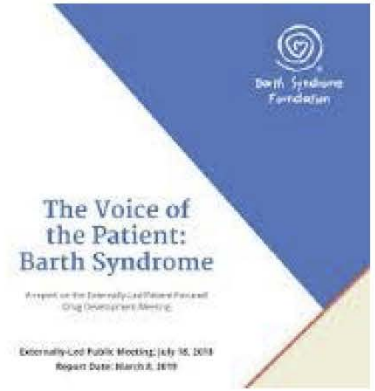
Gastrointestinal signs and symptoms
- Eating difficulty (n=4, 26.7%)
- Eating selectivity (n=3, 20.0%)
- Vomiting (n=3, 20.0%)

Immune system signs and symptoms
- Neutropenia (n=12, 80.0%)
- Infection (n=9, 60.0%)

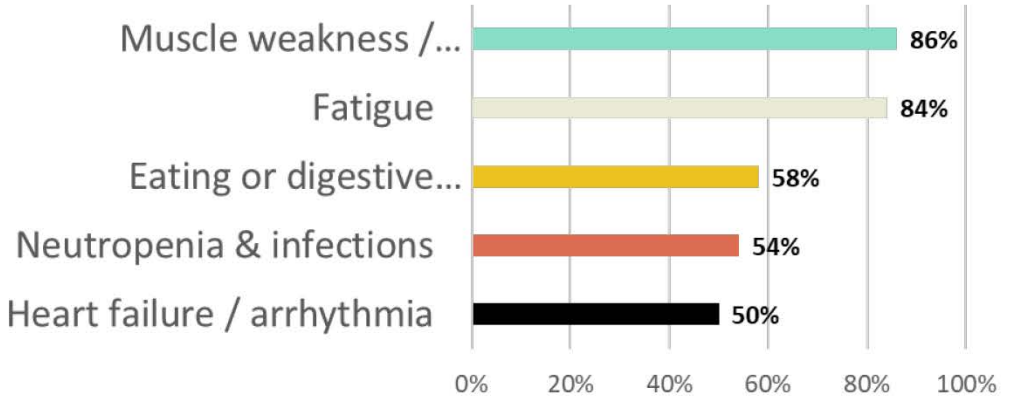
Pain signs and symptoms
- Muscle pain (n=6, 40.0%)
- General pain (n=3, 20.0%)
- Joint pain (n=2, 13.3%)

Sensory signs and symptoms
- Blurry vision (n=2, 13.3%)

Physical signs and symptoms
- Fatigue/tiredness (n=15, 100.0%)
- Muscle weakness (n=12, 80.0%)
- Physical developmental delay (n=4, 26.7%)
- Low muscle tone (n=4, 26.7%)
- Shortness of breath (n=5, 33.3%)
- Mouth sores (n=5, 33.3%)
- Fever (n=2, 13.3%)
- Inability to regulate body temperature (n=2, 13.3%)
- Dizziness/lightheadedness (n=5, 33.3%)
- Syncope (n=2, 13.3%)
- Foot deformities (n=2, 13.3%)
- Bone weakness (n=2, 13.3%)
- Scoliosis (n=3, 20.0%)
- Osteoarthritis (n=2, 13.3%)



% OF RESPONDENTS REPORTED SIGNIFICANT SYMPTOM



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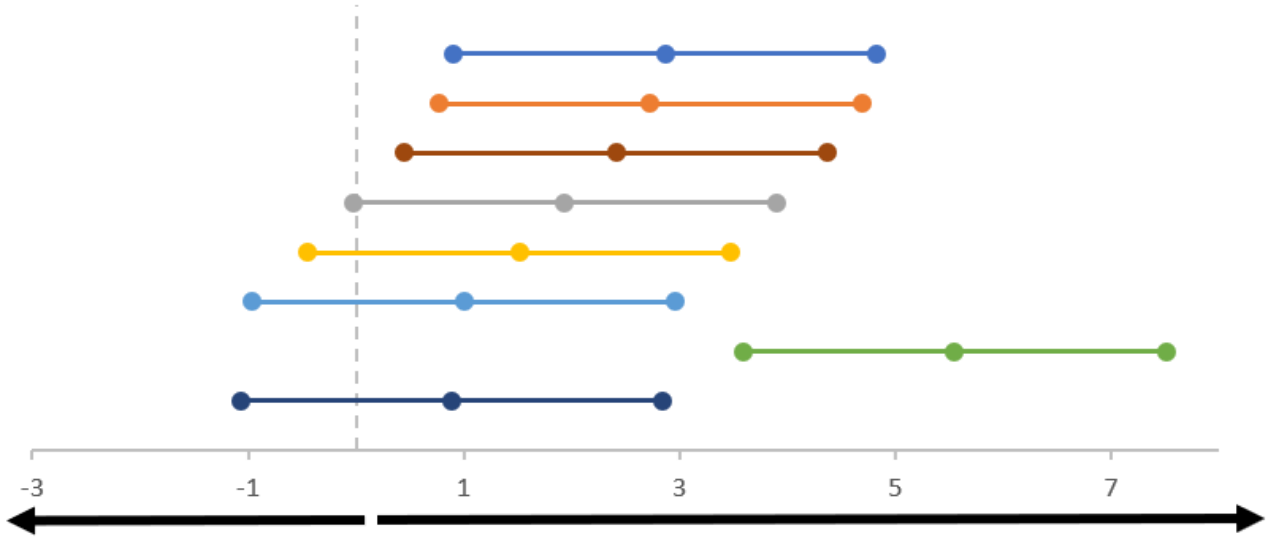
Greater magnitude of improvement with longer duration of dosing during OLE

Barth Phase 2 – Week 36 Open-Label Extension Changes from Part 1 Baseline

Summary of Treatment Effect Change from Baseline: N=8

Endpoint	Mean (95% CI)	p-value*
6MWT (meter)	95.9 (30.3, 161.5)	0.024
BTHS-SA Total Fatigue (mean score)	-2.1 (-3.6, -0.6)	0.031
PGI of Barth Syndrome Symptoms (mean score)	-0.6 (-1.1, -0.1)	0.049
CGI of Barth Syndrome Symptoms (mean score)	-0.6 (-1.3, 0.0)	0.095
PROMIS Fatigue (mean score)	-5.6 (-12.8, 1.6)	0.173
SWAY Balance (mean score)	4.7 (--4.5, 13.9)	0.350
Muscle Strength by HHD (Newtons)	56.0 (36.2, 75.8)	0.001
5XSST (seconds)	-1.1 (-3.4, 1.3)	0.219



Treatment Effect Rescaled to a T-score and Standard Error Unit of 1

P-values represent a t-test for matched pairs, comparing mean at baseline to mean at Week 36.

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Strategies to Evaluate Open-label Extension Data

✓	Comparison to Part 1 Placebo Control	OLE improvements in functional endpoints exceed placebo in double-blind portion of trial
✓	Comparison to Published Natural History	OLE improvement in 6MWT exceed published natural history
	Comparison to Patient as Own Control	To be assessed pursuant to pre-specified protocols
	Comparison to Virtual Match Control Across Functional Assessments	To be assessed pursuant to pre-specified protocols
X	[Randomized Withdrawal	Patients, advocacy and investigator opposed to this approach; potentially disease modifying changes and small number of patients present scientific and logistical challenges

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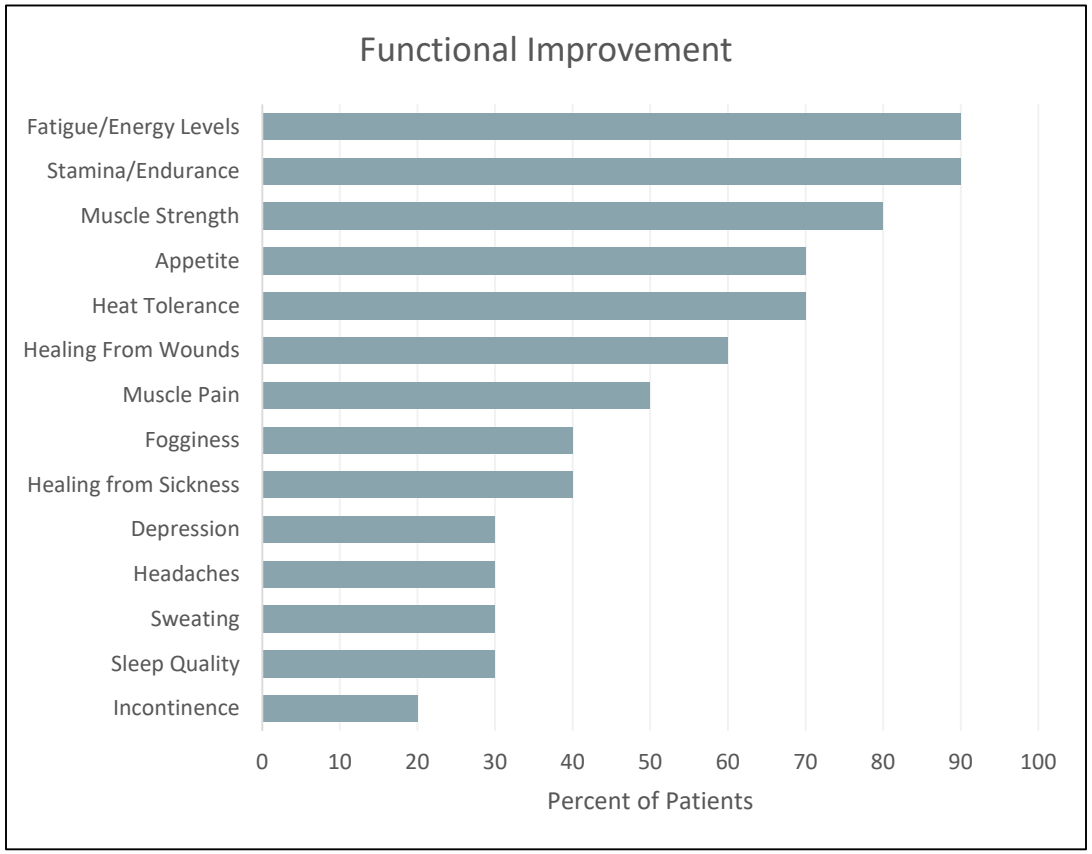
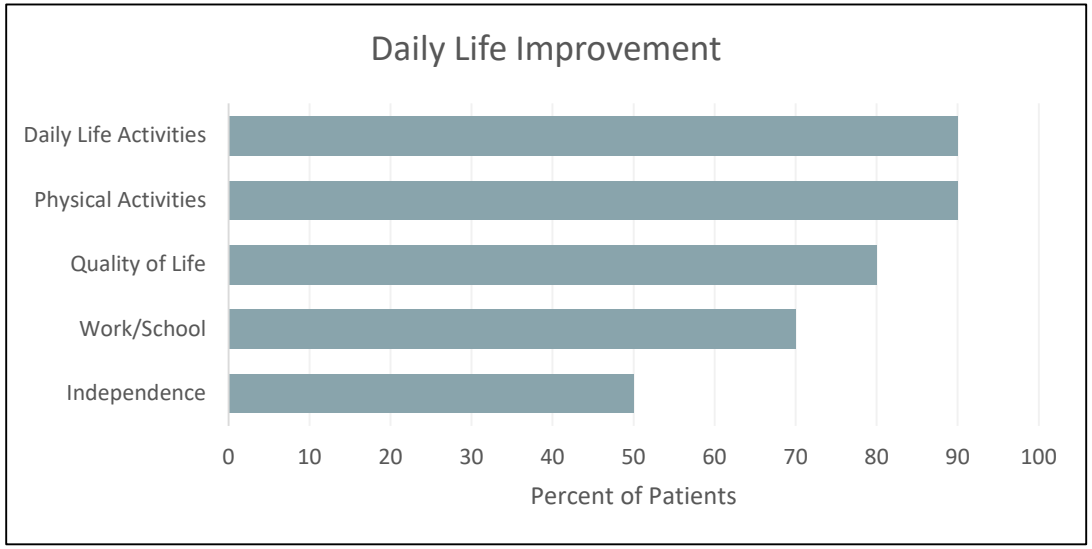
Patient perception of change

Prospectively defined video protocol to collect evidence of clinical meaningfulness to patients
Most patients report improvement in hallmark symptoms of fatigue, stamina, muscle strength



Represents improvements reported by participating subjects (and/or their caregivers) (n=10 subjects)



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Primary Mitochondrial Myopathy Program: Key Clinical Insights

Genetic defect in mitochondrial or nuclear DNA leading to predominantly myopathic symptoms (debilitating fatigue, skeletal muscle weakness, exercise intolerance). At least two additional organ systems are typically also affected.

- Use of primary endpoint family to assess effect on two hallmark sequelae: fatigue and exercise intolerance
  - Patient feedback indicates that fatigue is the most bothersome symptom
    - Limited ability to perform activities of daily living
    - Fatigue is not limited to activities
    - Off the shelf instruments not ideal for assessing fatigue so a PRO was developed
  - 6MWT to assess exercise intolerance
  - Phase 3 enrichment based on performance of the 6MWT
    - Lower walkers appear to respond more favorably in P1/2 and P2 trials
    - Potentially less variability
    - Creates an enrollment challenge due to higher screen failure rate
- Adjudication committee to confirm that myopathy related to genotype
  - Expert opinion helpful to ensure some degree of homogeneity in syndromes where significant heterogeneity exists

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Primary Mitochondrial Myopathy Program: Key Operational Insights

- Pre-trial registry
  - Enhances speed of enrollment
  - Helps to characterize natural history – e.g., suggests ~19m decline in 6MWT over ~12m period but no increase or decrease in fatigue
- Clinical Operational Challenges:
  - Subject visits to sites and sequence of performing certain assessments may exacerbate fatigue and exercise intolerance
  - Sites have been required to help manage travel to sites

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Extensive Interactions with FDA to Gain Alignment

1 pre-NDA, 1 EOP2, 1 F2F Type C, 2 WRO Type C, Extensive Correspondence, SAP review

✓	Basket Design	Pre-IND meeting	Alignment re novel “basket design” to drive toward clinical homogeneity
✓	6MWT primary	EOP2 & subsequent Type C meeting	Alignment re 6MWT as primary efficacy endpoint; enrichment for more impaired subjects more likely to respond
✓	Fatigue as part of primary endpoint family	Type C meeting & COA staff engagement	Suitability of Fatigue PRO as basis for approval; validation of novel PRO
✓	Phase 3 duration	Type C meeting	Recommended 6 mos. to demonstrate durability
✓	Patient population	Type C meeting	PMM requires genetic PMD + clinical diagnosis; stratification by subsets of mutations
✓	CMC	Type C meeting and subsequent correspondence	Engagement regarding drug product and device
✓	SAP & Hochberg	Type C meeting and SAP review	Alignment re primary endpoint family analysis

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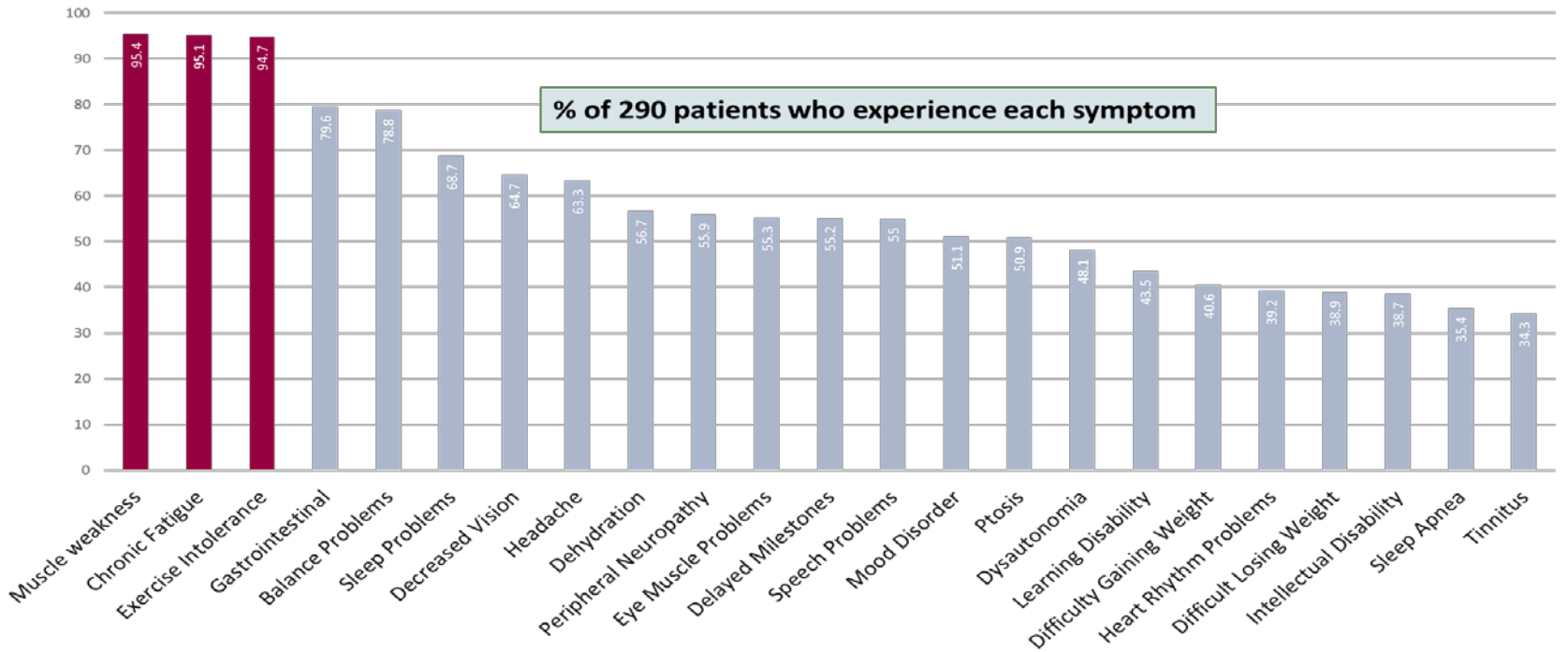
Primary mitochondrial myopathy

Myopathic Symptoms = Most Common Symptoms of Primary Mitochondrial Disease



Zolkipli-Cunningham, et. al., https://doi.org/10.1371/journal.pone.0197513

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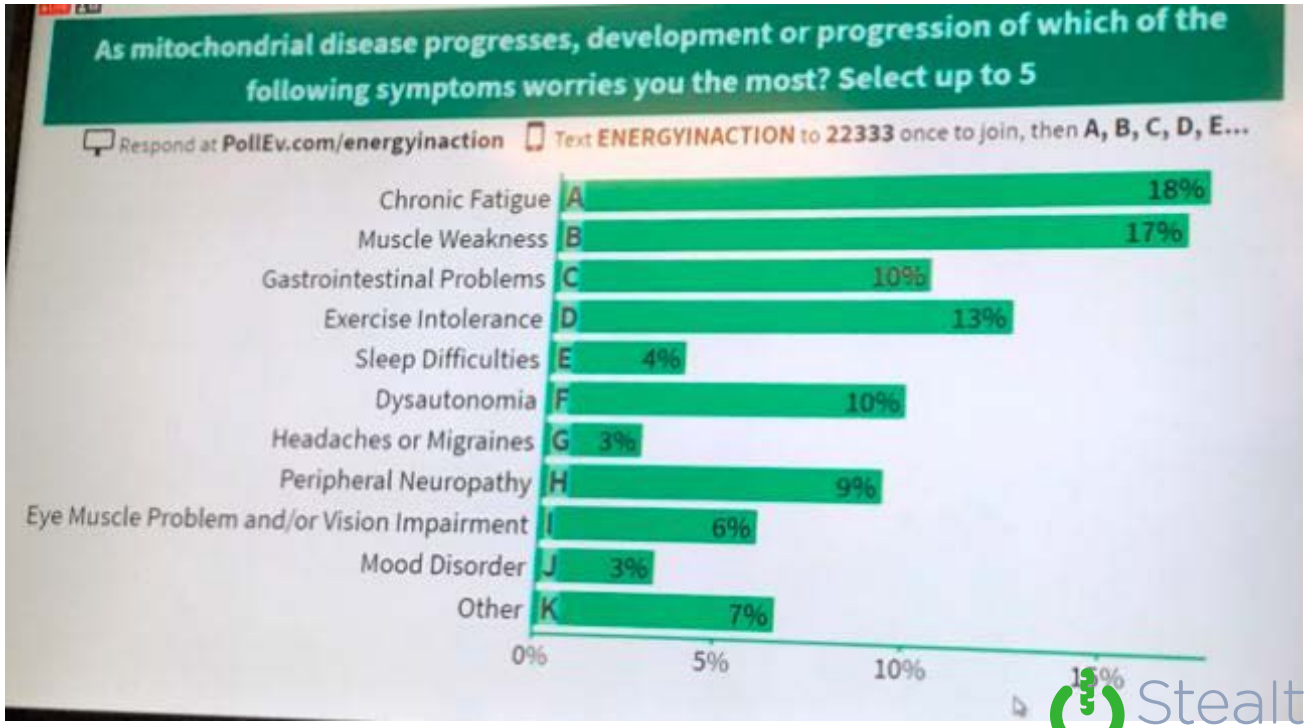
Patient reported outcome assessments: PMMSA

Fatigue and muscle weakness aligned with PFDD most worrisome symptoms

Primary Mitochondrial Myopathy Symptom Assessment (PMMSA)

	Not at all	Mild	Moderate	Severe
1. During the past 24 hours, how severe was your worst feeling of tiredness at rest?	☐	☐	☐	☐
2. During the past 24 hours, how severe was your worst feeling of tiredness during activities?	☐	☐	☐	☐
3. During the past 24 hours, how severe was your worst feeling of muscle weakness at rest?	☐	☐	☐	☐
4. During the past 24 hours, how severe was your worst feeling of muscle weakness during activities?	☐	☐	☐	☐
5. During the past 24 hours, how severe were your worst balance problems?	☐	☐	☐	☐
6. During the past 24 hours, how severe were your worst vision problems?	☐	☐	☐	☐
7. During the past 24 hours, how severe was your worst abdominal discomfort (feeling nauseous, bloated, or in pain)?	☐	☐	☐	☐
8. During the past 24 hours, how severe was your worst muscle pain?	☐	☐	☐	☐
9. During the past 24 hours, how severe was your worst numbness?	☐	☐	☐	☐
10. During the past 24 hours, how severe was your worst headache?	☐	☐	☐	☐

Energy in Action



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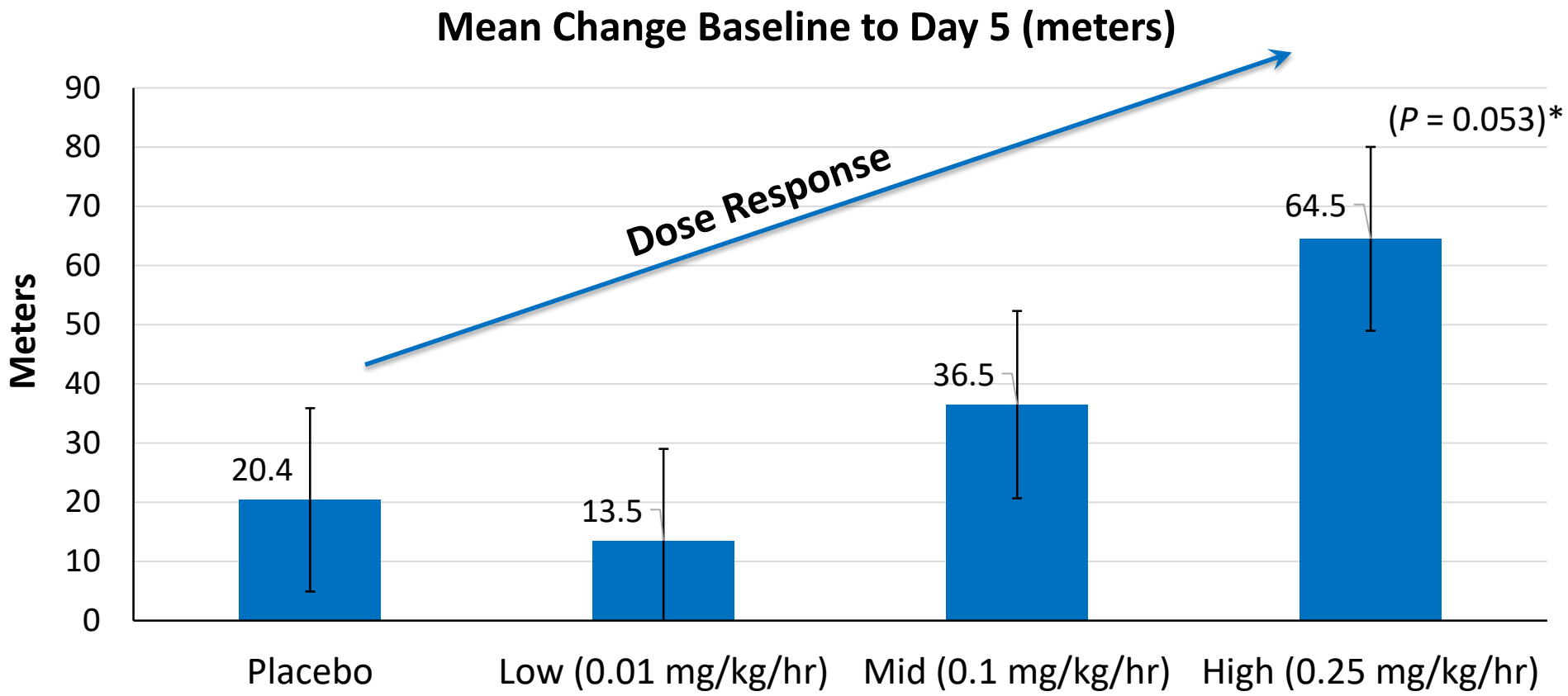
MMPOWER: Primary Endpoint Change in Distance Walked at Day 5



* High dose vs Placebo

Karaa A, et al. MMPOWER: Randomized dose-escalation trial of elamipretide in adults with primary mitochondrial myopathy, Neurology Mar 2018, 10.1212/WNL.0000000000005255

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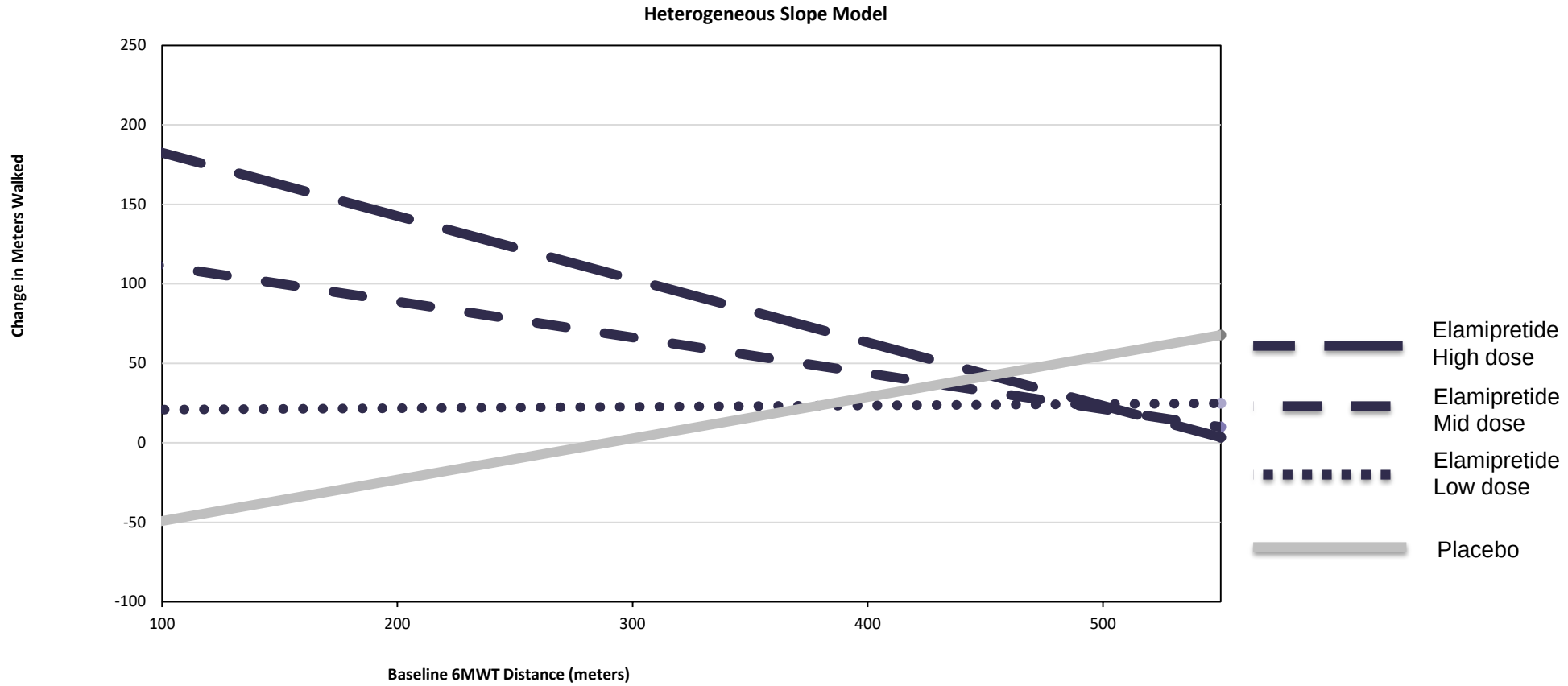
Larger magnitude of effect in patients with lower baseline walk distances

Change in Six Minute Walk Distance at Day Five*



* Data in the figure reflects certain post hoc adjustments for gender and baseline differences among subjects

** R-squared of adjusted model: 0.42; R-squared of primary analysis model (baseline and treatment only): 0.18.

Karaa, UMDF, 2016

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MMPOWER-3: adjudication committee classification

FDA recommended stratification by subgroups

Classification*	**MMPOWER-2**	**MMPOWER-3**
mtDNA: impair mitochondrial protein synthesis in toto	63%	74%
mtDNA: affect the subunits of the respiratory chain	17%	0.4%
nDNA: genes encoding subunits or ancillary proteins of the respiratory chain	3%	3%
nDNA: defects of intergenomic signaling	10%	22%
nDNA: alterations of mitochondrial motility or fission	7%	0

- Expert committee unanimously approved PMM diagnosis for each patient
- Stratification by classification category

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Key insights from both programs

- Involve patients in clinical trial planning
  - Elucidation of symptoms most problematic for patients
- Patient advocacy groups are critical for trial success
  - Scientific and medical advisory board insights
  - Foster awareness of trial recruitment
  - Hosted patient webinars
- Intense investigator engagement is critical
  - Solicited feedback about protocol design
  - Frequent site visits to encourage enrollment and assess quality
  - Some sites have little clinical research experience so intense monitoring is essential
- Collaboration with FDA is essential
  - Alignment on endpoints, including PRO development
  - Strategies for interpreting data from small datasets

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Developing novel therapies to help patients suffering from unmet medical needs

Be mighty…our patients are waiting

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