An interventional clinical trial to evaluate the role of elamipretide in individuals with Barth Syndrome

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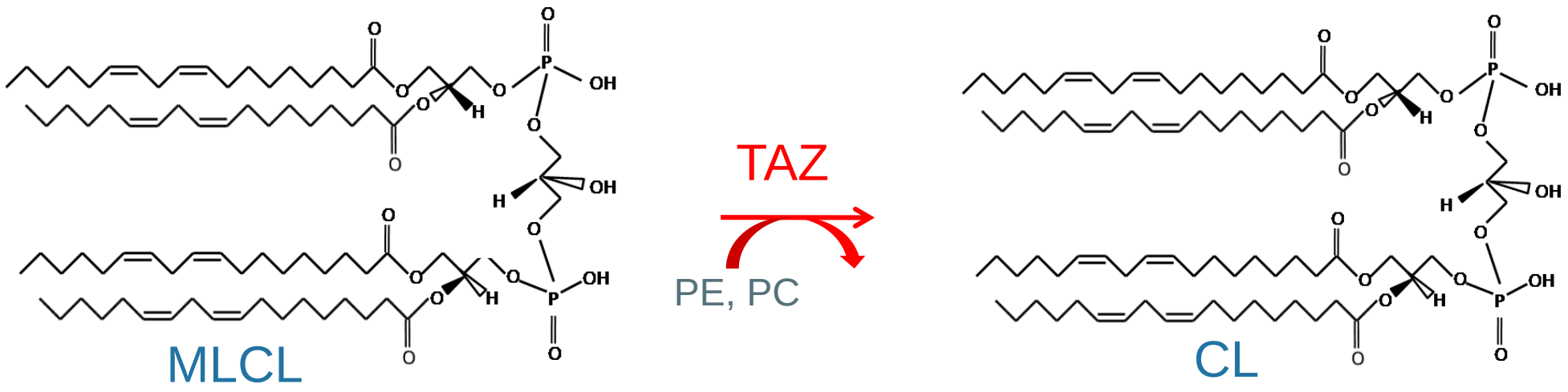
Disclosures

- Dr. Vernon has disclosed a financial relationship with Stealth BioTherapeutics
  - Funding for the SPIBA clinical trial program in Barth Syndrome

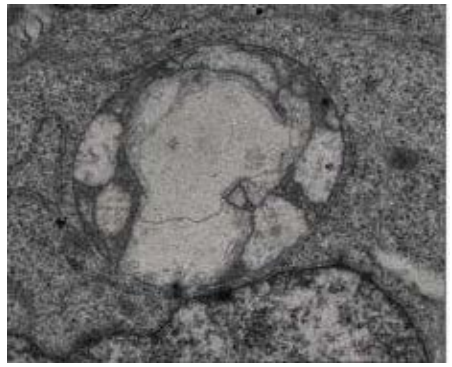
Barth Syndrome: A Rare, X-Linked Disorder

- Caused by pathogenic variants in tafazzin (*TAZ*)
- Acyltransferase
  - Final step in production of mature cardiolipin
  - Defects in TAZ lead to accumulation of monolysocardiolipin (MLCL) and reduction in remodeled, mature cardiolipin (CL)



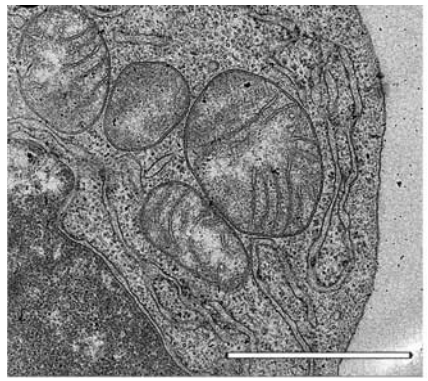
Cardiolipin: A mitochondrial phospholipid with many roles

- Located on the inner mitochondrial membrane (IMM)
  - maintaining mitochondrial structure
  - organizing IMM protein complexes
  - apoptosis
- Abnormalities implicated in multiple diseases
  - Diabetes, obesity, heart disease
  - BTHS: Only known Mendelian disorder of CL metabolism



BTHS Mitochondria

- Loss of IMM organization
- Decrease in respiratory supercomplex formation
- Inefficient electron flow and ATP generation



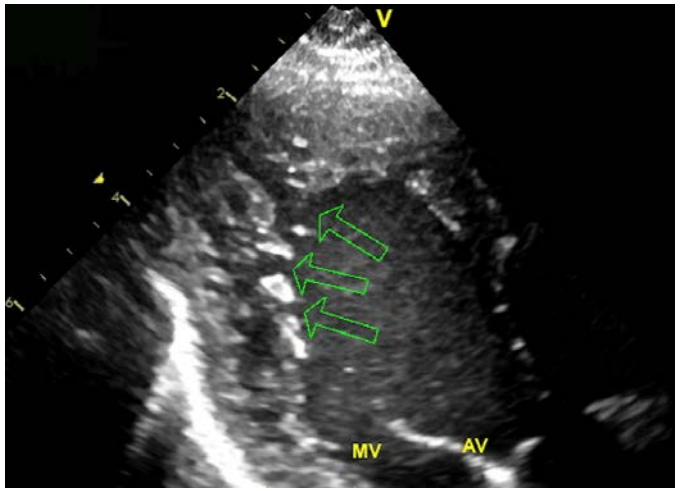
Healthy Mitochondria

- IMM well organized
- Respiratory supercomplexes intact
- Efficient electron flow and ATP generation

1. Shidoji Y, et al. *Biochem Biophys Res Commun.* 1999;264:343-347. 2. Birk AV, et al. *Br J Pharmacol.* 2014;171:2017-2028. 3. Zhang M, et al. *J Biol Chem.* 2002;277:43553-43556. 4. Xu Y, et al. *Nat Chem Biol.* 2016;12:641-647.
5. Saric A, et al. *Front Genet.* 2016;6:359. 6. Kulik W, et al. *Clin Chem.* 2008;54:371-378. 7. Schlame M, et al. J Am Coll Cardiol. 2003;42:1994-1999, Images Acehan D, et al, Laboratory Investigation (2007) 87, 40–48

Barth Syndrome: Clinical features

- 1 in every 300,000–400,000 births
  - Presents during infancy/early childhood
  - 50% of deaths <1y of life
  - Life expectancy is foreshortened for many
- Cardiac disease
  - Dilated cardiomyopathy +/- hypertrophic component
  - Left Ventricular non-compaction
  - Waxing and waning severity of cardiac dysfunction
- Intermittent Neutropenia
- Skeletal muscle weakness
- Growth abnormalities



Ferreira C, et al. https://www.ncbi.nlm.nih.gov/books/NBK247162. October 9, 2014, Hastings, et al. Clin Dysm, 2009; 18(4): 185-7

Obstacles for developing therapeutics in BTHS

- Ultra-rare genetic condition
- Lack of prospective natural history studies
  - Small cohorts
- Difficulty with clinical targets for measurement of outcome
  - waxing and waning of cardiac function and neutropenia
  - quantitative measurements often in the normal range
- No biomarkers correlating to clinical status
- No known genotype/phenotype correlation

Thompson WR, et al. *Genet Med.* 2016;18:1001-1010.

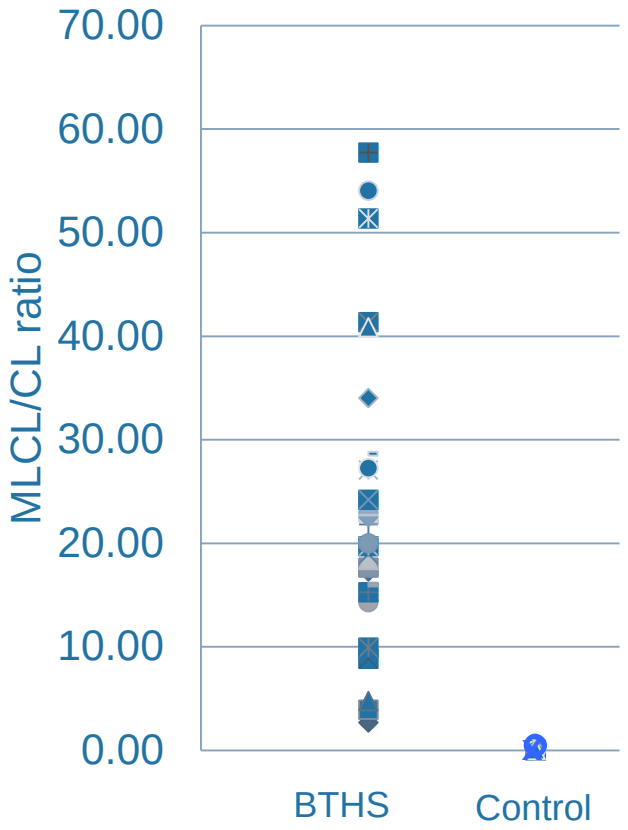
Defining the BTHS phenotype: Multidimensional cross sectional clinical study

- Define phenotypic spectrum of disease and look for correlations between quantitative data across 34 individuals with BTHS
  - Cardiac size and function
  - Skeletal muscle strength
  - Endurance (6 minute walk test)
  - Quality of life
  - MLCL/CL
  - Metabolomics analysis
    - identify further discriminating biochemical features

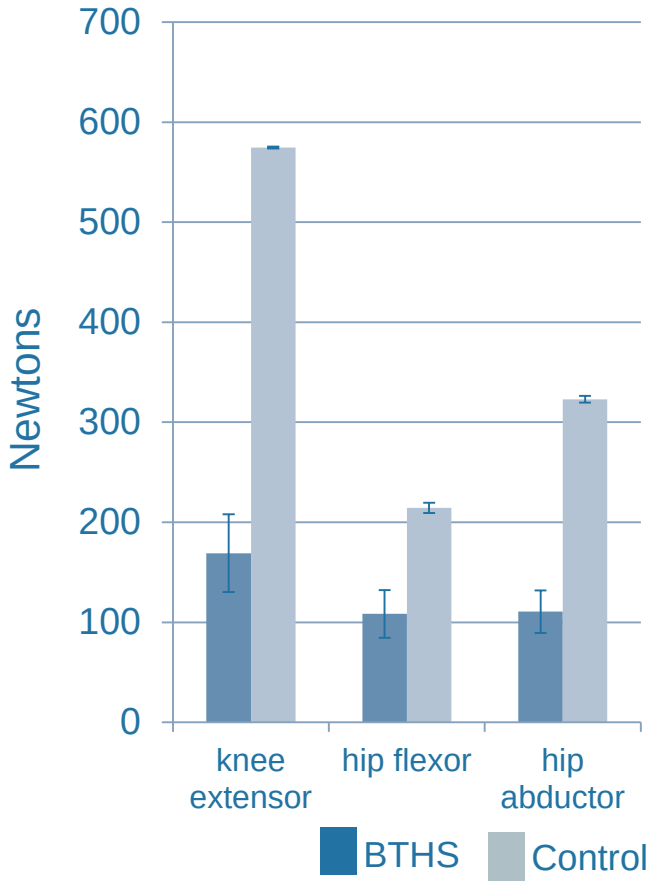
Thompson WR, et al. *Genet Med.* 2016;18:1001-1010.

Defining the BTHS phenotype

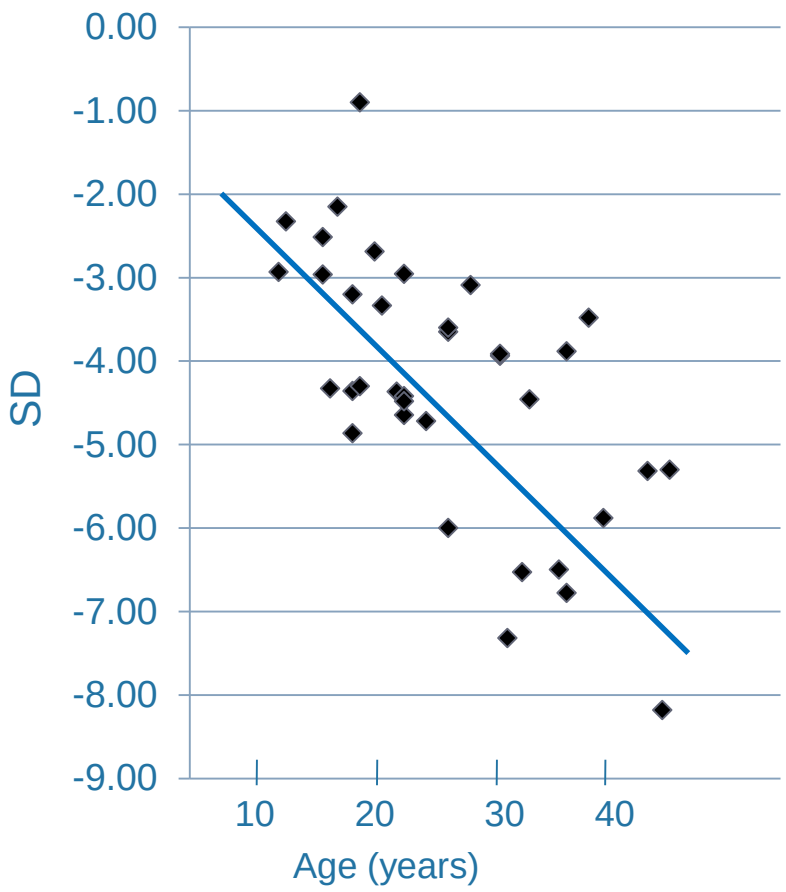
Cardiolipin Ratio



Lower Extremity Strength



6MMWT Distance



- 6Thompson WR, et al. *Genet Med.* 2016;18:1001-1010.

MLCL:CL Ratio Linked to Morbidity

- Regression analysis performed to identify relationships between metabolite measurements and quantitative clinical outcomes

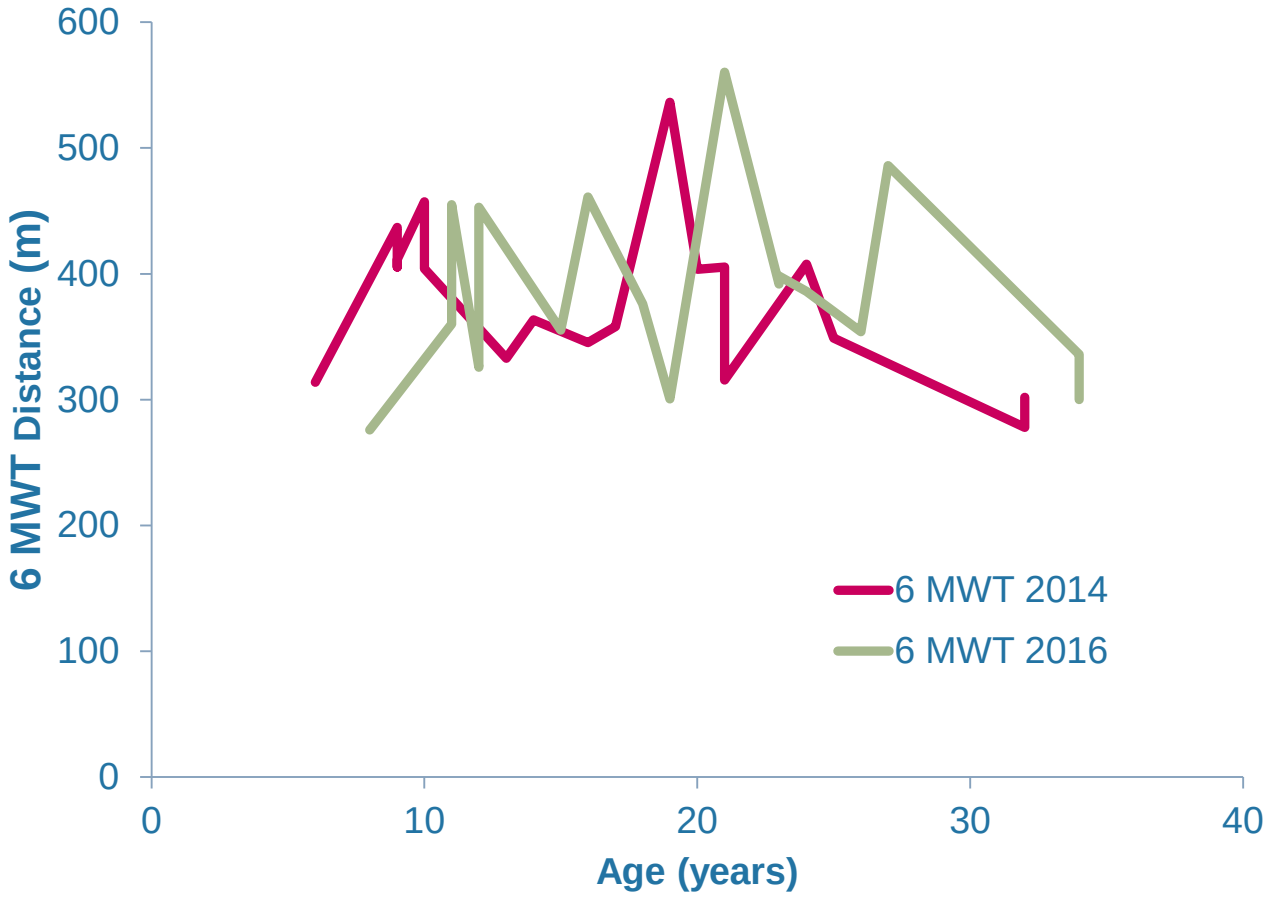
MLCL:CL Ratio
• Inversely correlates with distance walked on the 6MWT (*P*=0.00014) • Increasing ratio correlates with increasing LVM (*P*=0.0374)
6MWT and LVM serve as independent clinical markers for therapeutic monitoring

Thompson WR, et al. *Genet Med.* 2016;18:1001-1010.

2-year longitudinal follow up study of 6MWT in 18 subjects

6MWT is statistically unchanged across the study population in a 2 year follow up study

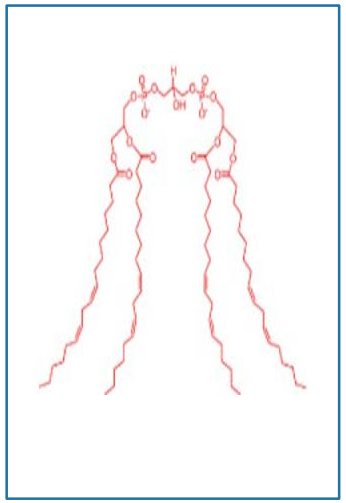
- 2014: average distance was 379±63 m (SD)
- 2016: average distance was 387.8 m ± 71 (SD)
- 1 individual had significant worsening, and 1 individual had significant improvement
  - Correlated to major health events in the interim time period



Hornby et al. Orphanet J Rare Dis. 2019 Jan 22;14(1):37

Elamipretide purported mechanism of action

Elamipretide is believed to diffuse across cell membranes and bind to cardiolipin in IMM



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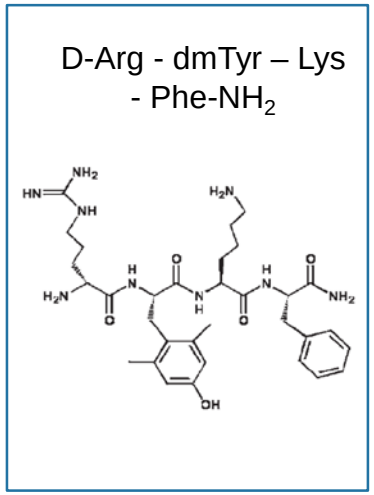

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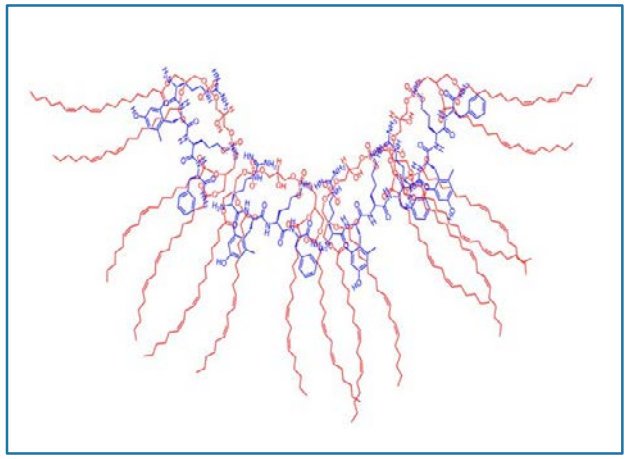


By binding to cardiolipin in the inner mitochondrial membrane (IMM), elamipretide is believed to stabilize cristae architecture and electron transport chain (ETC) structure during oxidative stress

Szeto HH. *Br J Pharmacol.* 2014;171:2029-2050.

TAZPOWER: Elamipretide in Patients With Barth Syndrome

Double-Blind Trial Results
&
Open-Label Extension Trial Results @ Week 36

TAZPOWER Study Design

12-Week Pivotal Trial Followed by Open Label Extension

Primary Endpoints

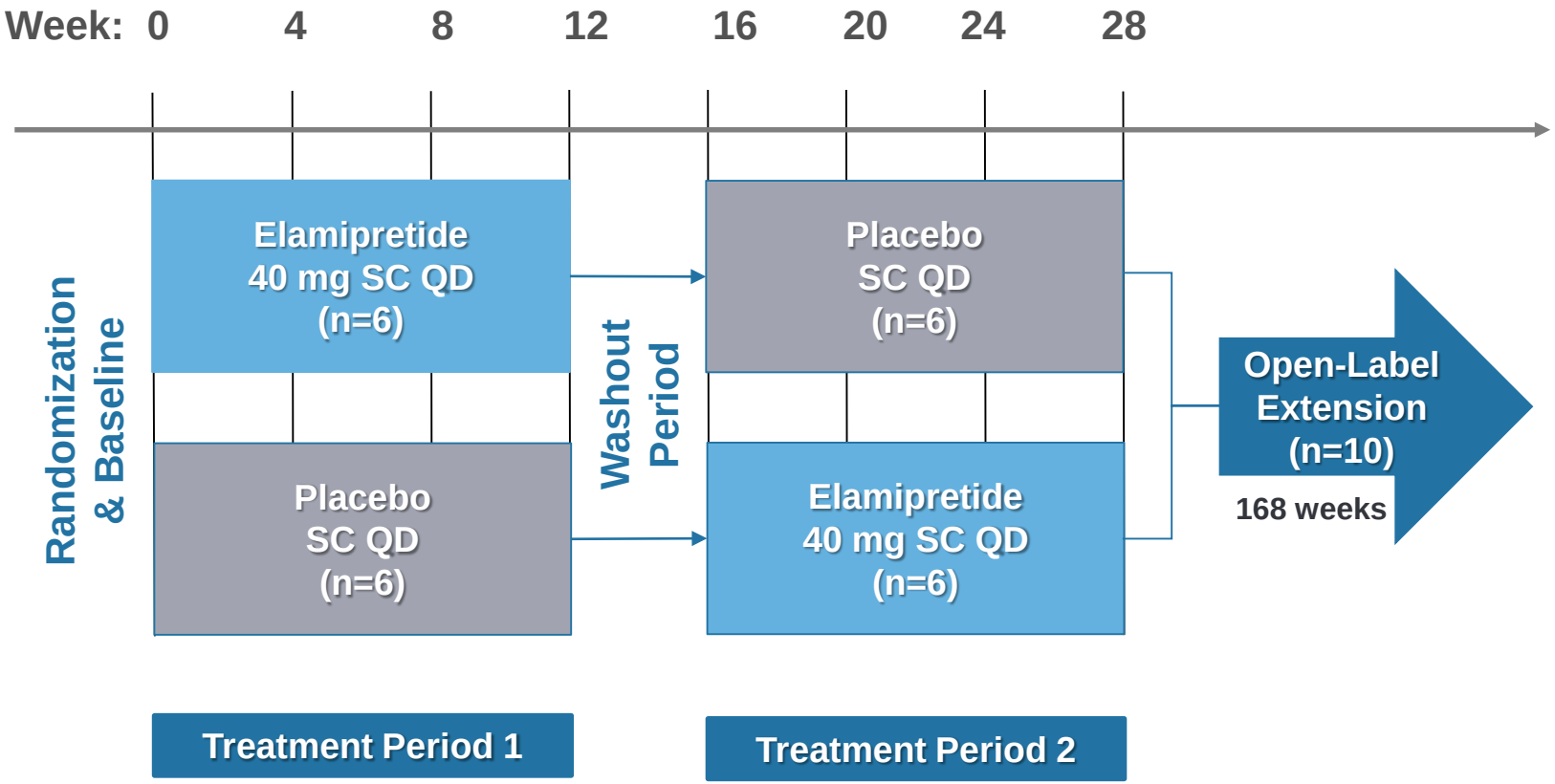
- **Distance walked (meters) on 6MWT**
- **Total fatigue score on BTHS-SA**

Secondary Endpoints

- **Functional assessments** (SWAY, HHD, 5XSST, CGI-S)
- **Patient-reported outcomes** (PGI-S, PROMIS Fatigue)
- **Safety and tolerability**
- **Laboratory assessments** (MLCL:L4-CL ratio)

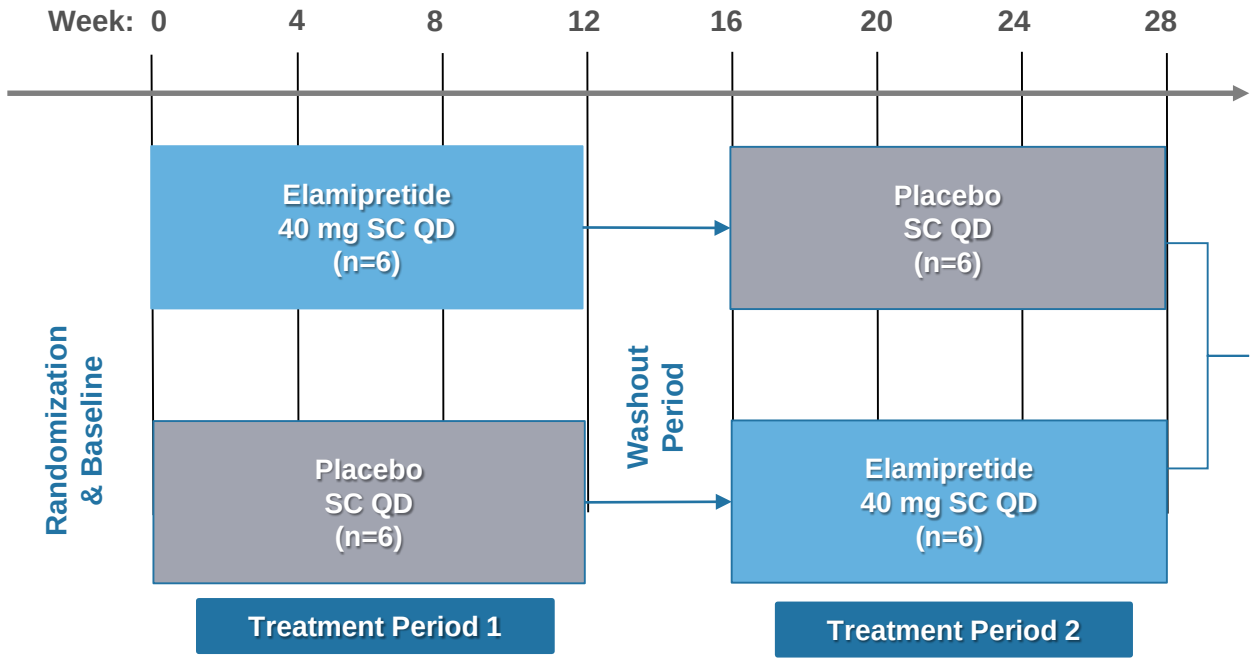
Key Inclusion Criteria

- Genetically confirmed BTHS
- Males age ≥12 y
- Ambulatory and impaired during 6MWT
- On stable medication for 30 d prior to baseline visit



Data on file. Stealth BioTherapeutics.

Summary of TAZPOWER Study Results



- At the end of the double-blind phase, statistical significance was not achieved on the primary endpoints
- Elamipretide provided clinically meaningful improvements in individual functional and patient-reported outcome measures
- Differential effect observed in patients with MLCL:L4-CL ratio below the median value of 17.3

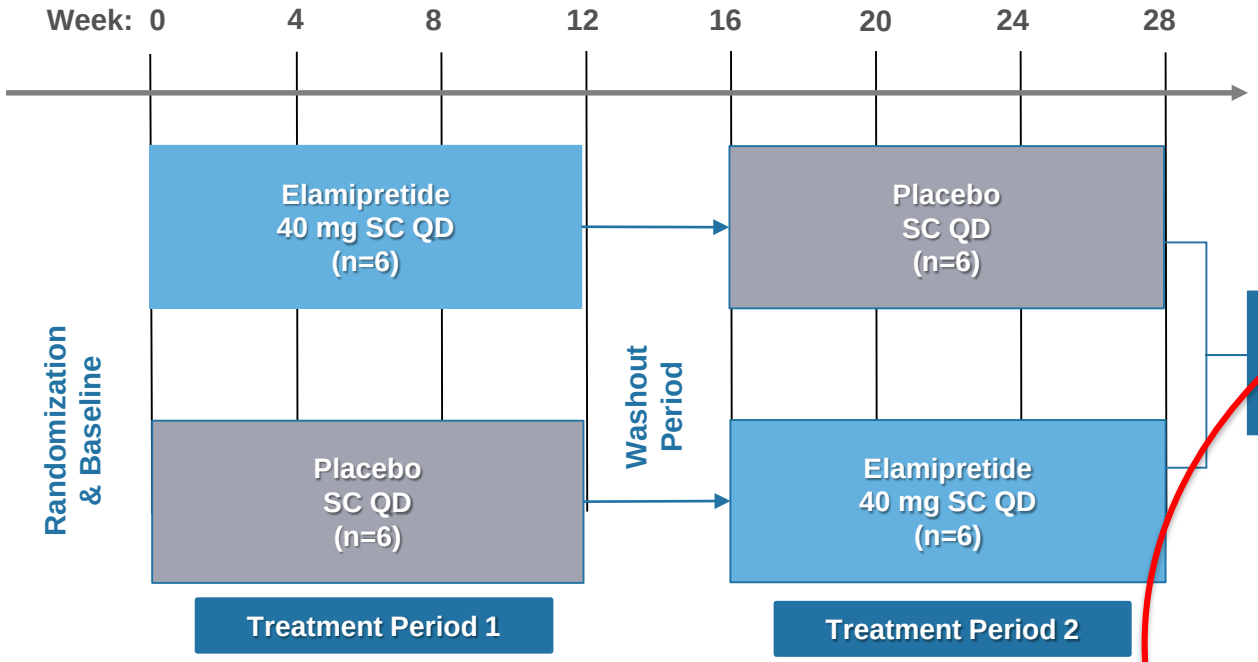
Data on file. Stealth BioTherapeutics.

Safety: Adverse Events

	Elamipretide 40 mg (N=12) n (%)	Placebo (N=12) n (%)
At Least One Adverse Events	12 (100.0)	10 (83.3)
Gastrointestinal disorders		
Aphthous ulcer	0	2 (16.7)
General disorders and administrative site conditions		
Injection site erythema	12 (100.0)	3 (25.0)
Injection site pain	9 (75.0)	4 (33.3)
Injection site induration	8 (66.7)	2 (16.7)
Injection site pruritus	8 (66.7)	2 (16.7)
Injection site bruising	3 (25.0)	0
Injection site urticaria	3 (25.0)	0
Medical device site irritation	2 (16.7)	1 (8.3)
Infections and infestations		
Bronchitis	2 (16.7)	1 (8.3)
Viral upper respiratory tract infection	1 (8.3)	2 (16.7)
Pharyngitis streptococcal	1 (8.3)	2 (16.7)
Injury, poisoning and procedural complications		
Ligament sprain	2 (16.7)	1 (8.3)
Nervous system disorders		
Headache	1 (8.3)	3 (25.0)

Data on file. Stealth BioTherapeutics.

Patient Transition into Open-Label Extension



Open-Label Extension up to 168 weeks

- 10 of 12 patients elected to continue in OLE
- All 10 patients have OLE week 12 assessments
- 8 of 10 patients have OLE week 24, 36, and 48 assessments

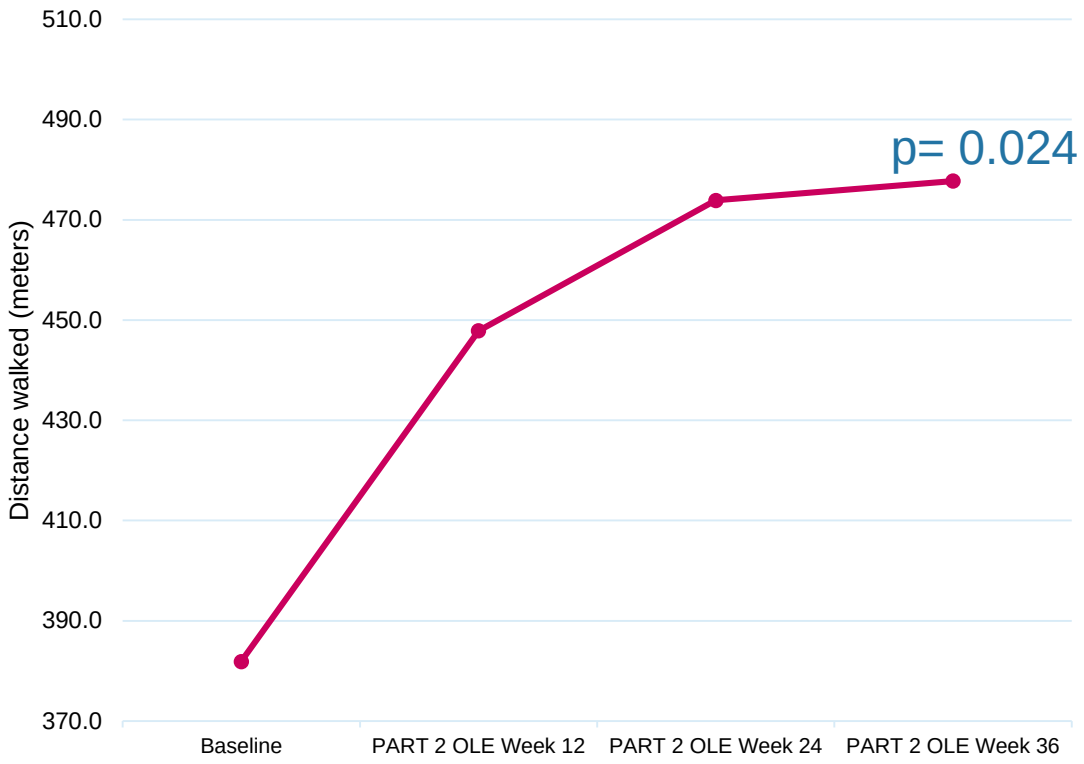
Assessments

- **Distance walked (meters) on 6MWT**
- **Total fatigue score on BTHS-SA**
- **Functional assessments** (SWAY, HHD, 5XSST, CGI-S)
- **Patient-reported outcomes** (PGI-S, PROMIS F-SF)
- **Safety and tolerability**
- **Laboratory assessments** (MLCL:L4-CL ratio)

Data on file. Stealth BioTherapeutics.

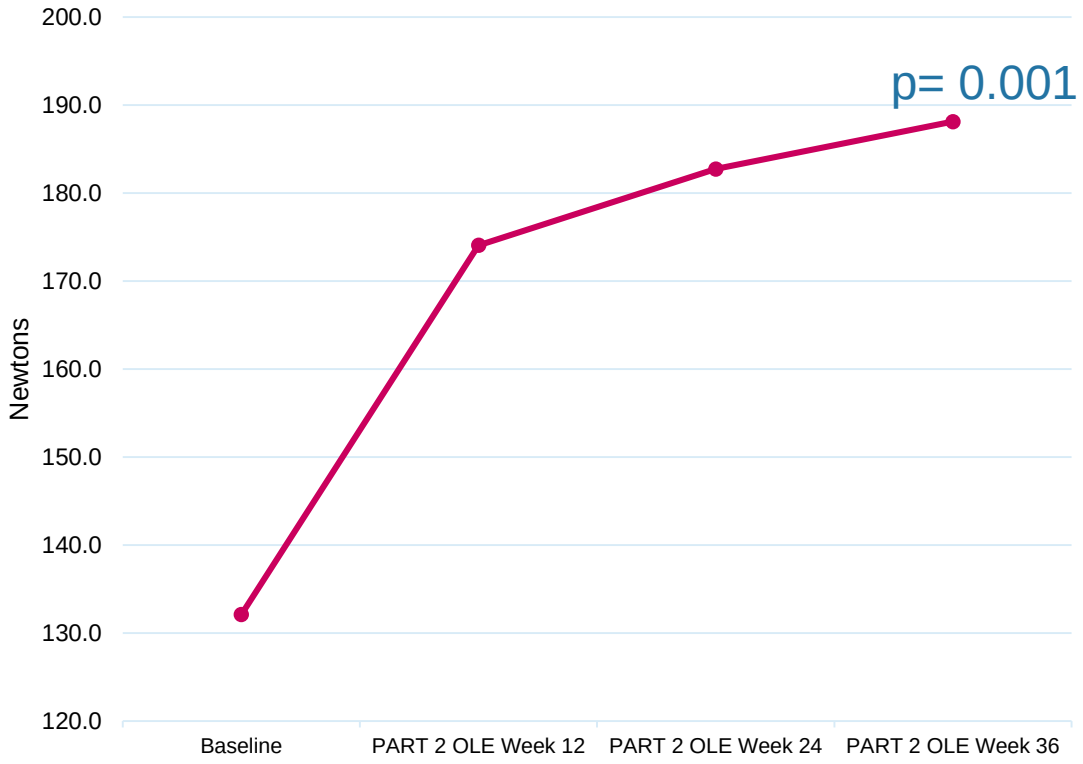
Efficacy in OLE: Functional Assessments

6-Minute Walk Test (6MWT)



Change in 6MWT Distance (meters) From Baseline			
n	Week 12	Week 24	Week 36
8	66.0 (±75.23)	92.0 (±74.03)	95.9 (±94.61)

Muscle Strength (newtons)

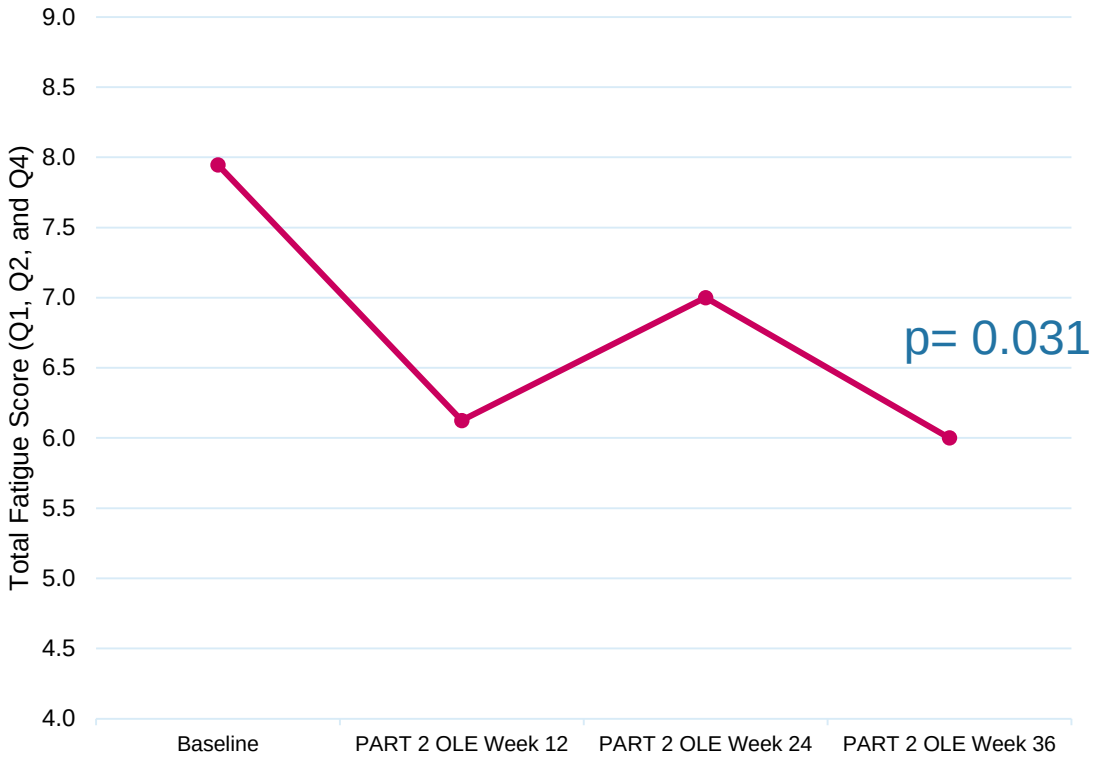


Change in Muscle Strength (newtons) From Baseline			
n	Week 12	Week 24	Week 36
8	42.0 (±30.33)	50.6 (±32.47)	56.0 (±28.56)

Data on file, Stealth BioTherapeutics.

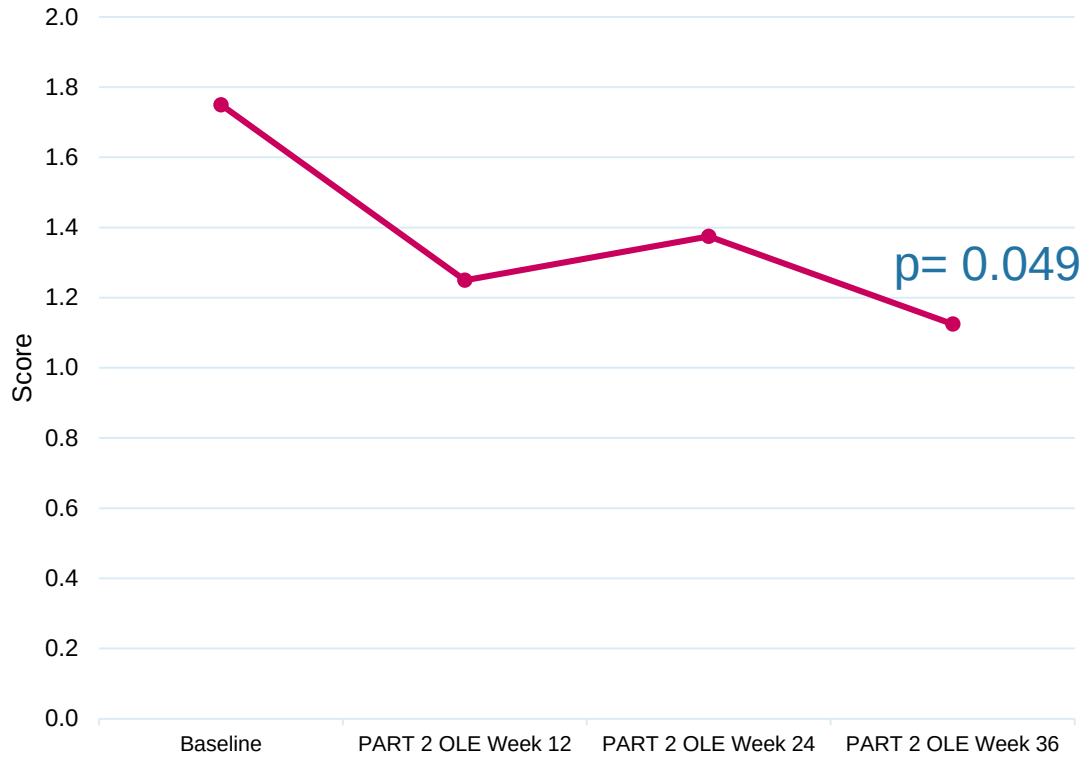
Efficacy in OLE: Patient-Reported Symptom Assessments

Barth-Syndrome Symptom Assessment (BTHS-SA)



Change in BTHS-SA From Baseline			
n	Week 12	Week 24	Week 36
8	-1.8 (±1.93)	-1.1 (±1.53)	-2.1 (±2.18)

Patient Global Impression (PGI) of Symptoms



Change in PGI of Symptoms From Baseline			
n	Week 12	Week 24	Week 36
8	-0.5 (±0.93)	-0.4 (±0.52)	-0.6 (±0.74)

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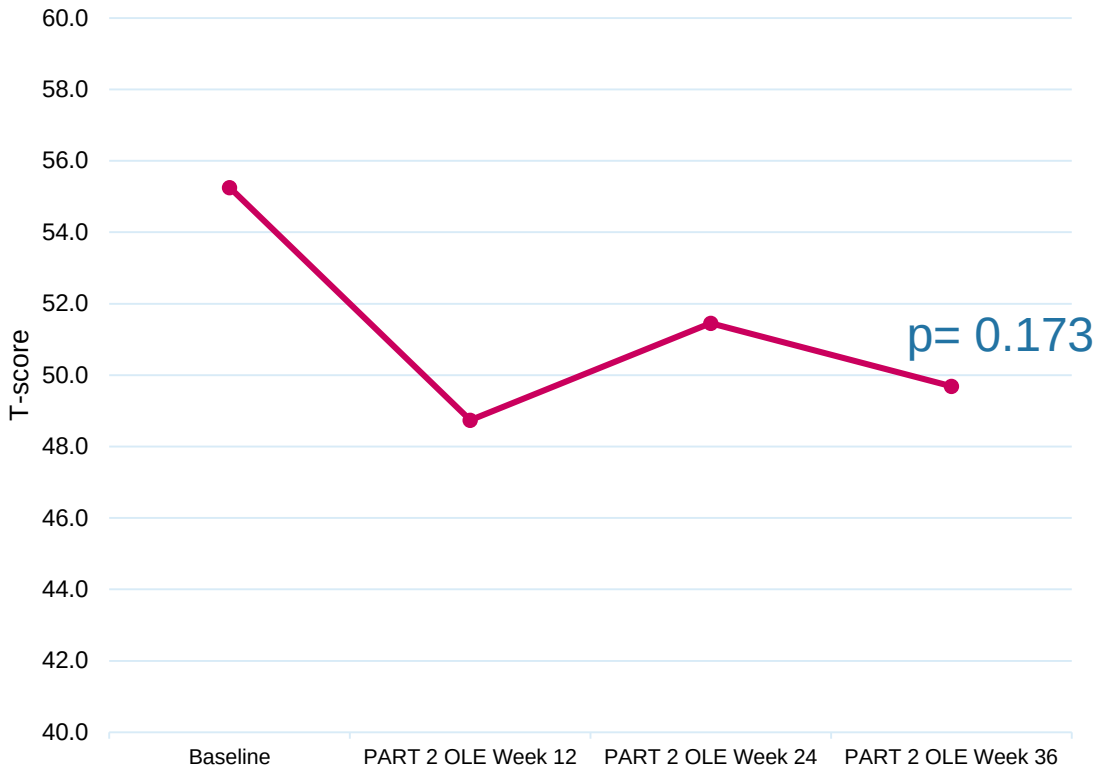
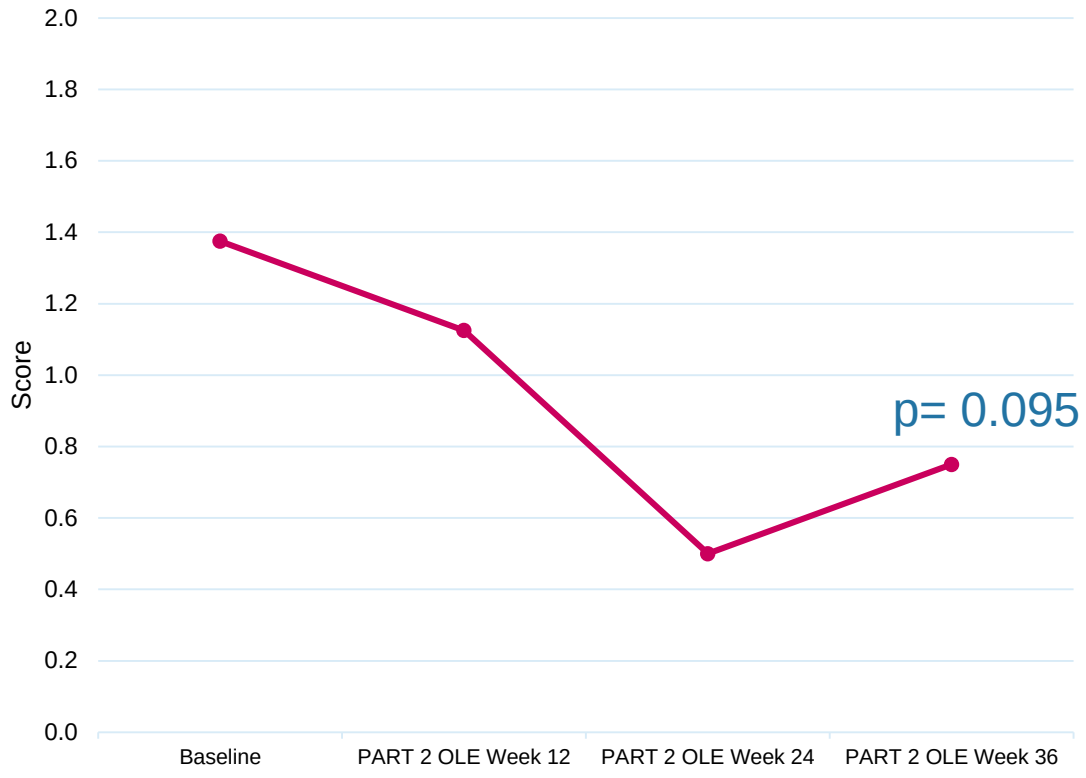
Efficacy in OLE: Symptom Assessments

PROMIS Short Form Fatigue



Change in PROMIS T-Score From Baseline			
n	Week 12	Week 24	Week 36
8	-6.5 (±9.44)	-3.8 (±6.29)	-5.6 (±10.38)

Clinician Global Impression (CGI) of Symptoms



Change in CGI of Symptoms From Baseline			
n	Week 12	Week 24	Week 36
8	-0.3 (±0.46)	-0.9 (±0.83)	-0.6 (±0.92)

Data on file. Stealth BioTherapeutics.

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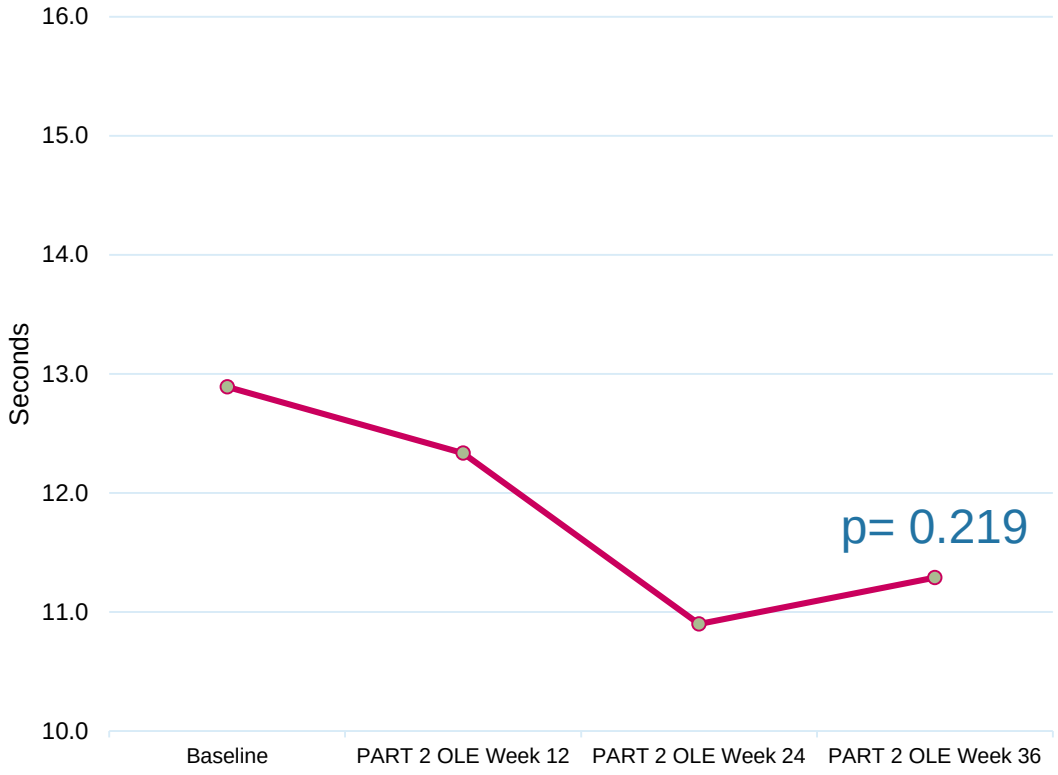
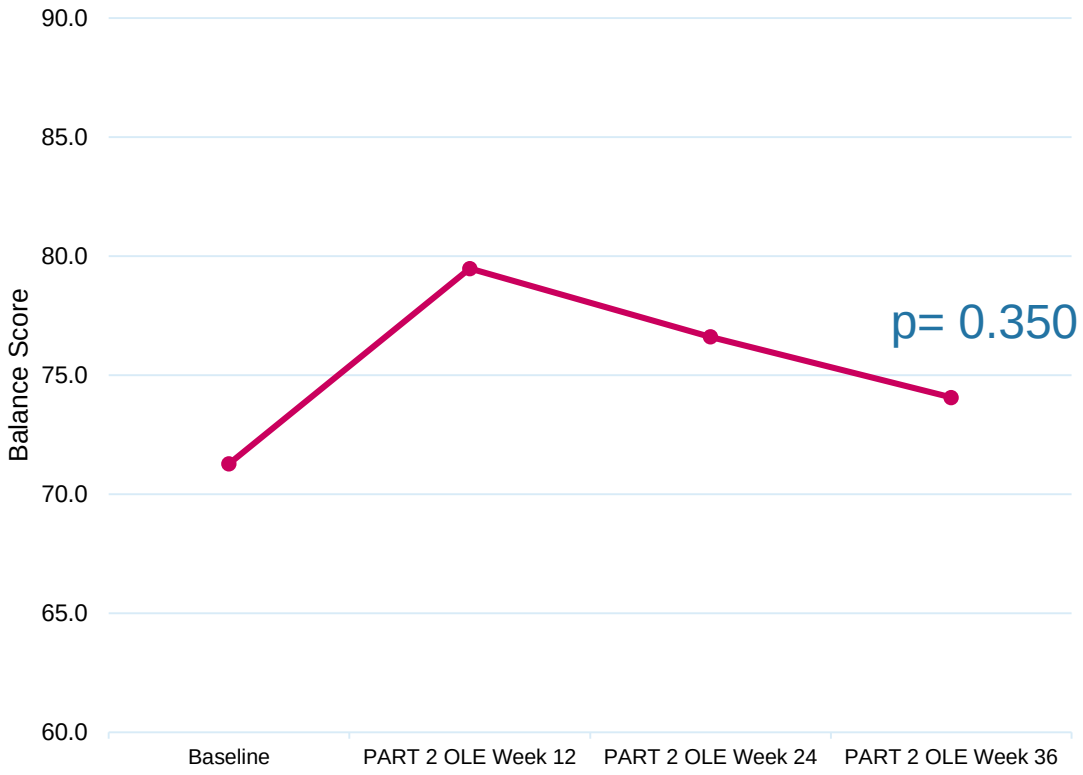
Efficacy in OLE: Functional Assessments

5-Times Sit-to-Stand (5XSST) [seconds]



Change in 5XSST (seconds) From Baseline			
n	Week 12	Week 24	Week 36
8	-0.6 (±3.31)	-2.0 (±2.83)	-1.1 (±3.35)

SWAY Balance Score



Change in SWAY Balance Score From Baseline			
n	Week 12	Week 24	Week 36
8	8.6 (±15.72)	6.5 (±7.70)	4.7 (±13.25)

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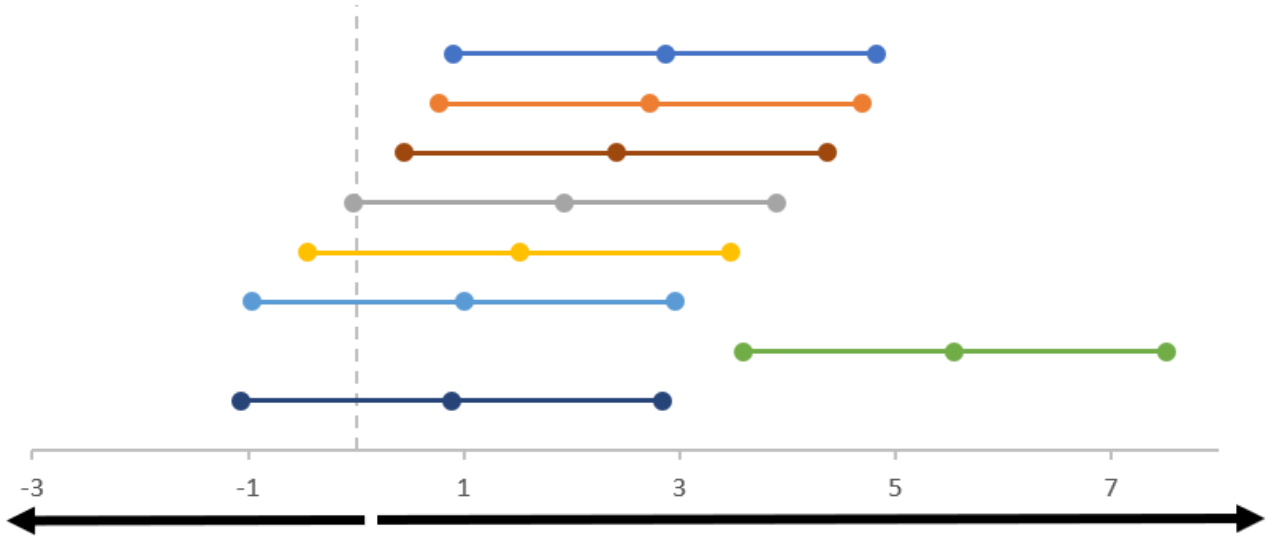
Summary of Treatment Effects: OLE Week 36

SPIBA-201 Part 2 Week 36

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 in Part 2 of SPIBA-201.

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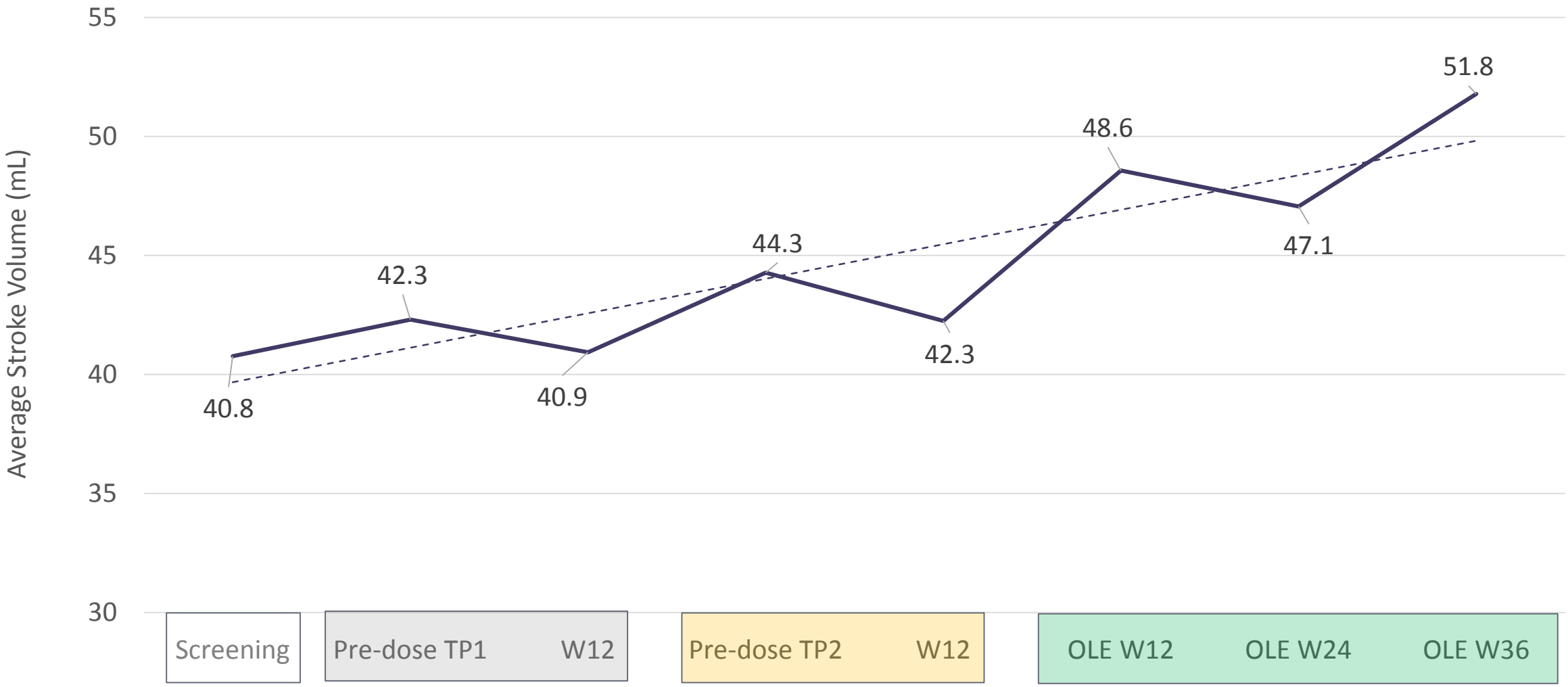
Additional outcome: Increased cardiac stroke volume



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Summary of observations

SPIBA 201, the first interventional clinical trial in Barth Syndrome

- 12-week double-blind phase
  - Statistical significance was not achieved on primary endpoints
  - However, subjects with lower MLCL:L4-CL ratios showed improvement compared to baseline on several endpoints
- Open Label Extension
  - Clinically significant improvements were observed in functional and PRO endpoints compared to baseline
  - Cardiac function data is suggestive of additional clinical benefit
- Elamipretide was generally well tolerated.
  - Most adverse events were mild to moderate in severity.
  - The most commonly reported adverse events include injection site reactions

BTHS: An example of advancing therapeutic development in a rare disease

- Thorough phenotyping
  - Cross sectional and longitudinal
  - Multidimensional
- Selection of quantitative endpoints
- Identification of potentially therapeutic compound
- Rational clinical trial design
  - Overcome limits of small participant pool
- Community engagement

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Barth Syndrome Foundation®

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Genetic Medicine

Stealth
BIOTHERAPEUTICS

And most importantly, the study participants and their families