Cardiovascular and Renal Drugs Advisory Committee Meeting

Elamipretide for the Treatment of Barth Syndrome

FDA Opening Remarks

October 10, 2024

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Barth Syndrome

- Rare, serious, mitochondrial disease caused by tafazzin mutation
- Tafazzin is needed for maturation of cardiolipin, a phospholipid that has a critical role in mitochondrial shape and energy production
- Disease manifestations include fatigue, skeletal and cardiac myopathy, neutropenia, premature death
- Treatment is supportive (e.g., heart failure therapy); there are no therapies specifically approved for Barth syndrome

Elamipretide

- Proposed Mechanism: Aggregation of cardiolipin, improving lipid packing in inner membrane, structure and function of energy-generating proteins
- Efficacy for Barth syndrome was assessed in:
  - SPIBA-201, Part 1 – a randomized, double-blind, placebo-controlled trial
  - SPIBA-201, Part 2 – a single-arm, open-label extension study
  - SPIBA-001 – an externally-controlled study
  - Other supportive studies (e.g., nonclinical studies)
- Efficacy endpoints included functional outcomes (e.g., 6-minute walk distance), fatigue, echocardiogram parameters, cardiolipin ratios

Focus of Today's Advisory Committee Meeting

- Can we conclude that elamipretide is effective for the treatment of Barth syndrome based on the available evidence?
- The advisory committee will hear differing perspectives on this question from the Applicant and FDA review team
- We ask the advisory committee to consider these two perspectives and provide independent, expert advice and recommendations based on the available evidence

Substantial Evidence of Effectiveness

Regulatory Standard for Establishing Effectiveness

Substantial Evidence of Effectiveness

- A drug's effectiveness must be established prior to approval based on substantial evidence[1]
- Substantial evidence generally requires at least two adequate and well-controlled (AWC) clinical investigations, each convincing on its own
- FDA may also determine that data from one AWC clinical investigation together with confirmatory evidence[2] may constitute substantial evidence
- FDA exercises regulatory flexibility within this framework

[1]FDA draft guidance for industry, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

[2]FDA draft guidance for industry, Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence

What is an Adequate and Well-Controlled Investigation?

- Provides the primary basis for determining whether there is substantial evidence
- Has characteristics that distinguish drug effect from other influences (e.g., bias)
  - Clear statement of objectives and summary of analysis methods
  - Design that permits a valid comparison with a control
    - Doesn't require placebo control (e.g., historical control may be acceptable when appropriate)
  - Subjects have the disease or condition being studied
  - Method of assignment to treatment, control minimizes bias to assure comparability
  - Adequate measures to minimize bias from subjects, observers, and data analysts
  - Methods of assessment of response are well-defined and reliable
  - Analysis of study results is adequate to assess the effects of the drug

21 Code of Federal Regulations (CFR) 314.126

What is Confirmatory Evidence?[1]

- Data that substantiate the results of one AWC investigation
- Less-persuasive AWC investigation may require more compelling confirmatory evidence

Examples:

- **Mechanistic or pharmacodynamic evidence**
  - Disease pathophysiology and drug's mechanism should be well-understood and the drug should directly target the major driver(s) of the pathophysiology
- **Evidence from a relevant animal model**
  - Depends on the similarity between the animal model and humans and evidence that efficacy in the animal model reasonably supports clinical benefits in humans
- **Real world data/evidence**
  - Depends on reliability and relevance of the data source, study design quality, use of appropriate prespecified statistical methods and analyses
- **Evidence from expanded access use**
  - May be considered if collected information has sufficient quantity and quality to be highly persuasive

What is Regulatory Flexibility?

- FDA can exercise regulatory flexibility regarding the kind and quantity of data required to meet statutory standards, considering disease severity, rarity, unmet need, feasibility, ethics
- Examples of regulatory flexibility include study design, number of studies, and statistical considerations for concluding effectiveness
  - In a rare disease the number of patients eligible for study may be so small that a second AWC investigation may be infeasible
  - For a rare disease with few patients, a p-value higher than the typical 0.05 threshold might be acceptable but should be prespecified and appropriately justified
  - Study designs that produce less certainty may be acceptable if a better design is not feasible or ethical
- However, in all cases FDA must conclude there is substantial evidence of effectiveness – the statutory standard remains the same

Discussion and Voting Questions

Advisory Committee Discussion Questions

1. Discuss whether SPIBA-201, Part 2 demonstrates that elamipretide is effective for the treatment of Barth syndrome (BTHS). Include in your discussion the interpretability of the single-arm, open label study design and the findings on:

    a. 6-minute walk distance
    b. Other functional outcomes: hand-held dynamometry, 5 times sit-stand-test, SWAY application balance.
    c. Echocardiography
    d. Patient reported outcomes (e.g., BTHS-Symptom Assessment total fatigue score, patient- and caregiver global impression scales)
    e. Monolysocardiolipin (MLCL) to tetralinoleoyl cardiolipin (CL) ratio (MLCL:CL ratio)

Advisory Committee Discussion Questions

2. Discuss whether SPIBA-001 demonstrates that elamipretide is effective for the treatment of Barth syndrome. Include in your discussion the interpretability of the externally-controlled study design and the findings on:

    a. 6-minute walk distance
    b. Other functional outcomes: hand-held dynamometry, 5 times sit-stand-test, SWAY application balance
    c. Echocardiography

3. Discuss the extent to which other data (e.g., nonclinical data or other clinical study results) support the effectiveness of elamipretide.

Advisory Committee Voting Question

4. Based on available evidence, do you conclude that elamipretide is effective for the treatment of Barth syndrome?

   Provide rationale for your vote.

   If you voted yes, specify the evidence of elamipretide's effectiveness.

   If you voted no, provide recommendations for additional data that may support a conclusion that elamipretide is effective.


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Cardiovascular and Renal Drugs Advisory Committee (CRDAC)
FDA Presentation

Efficacy Assessment of Elamipretide for Barth Syndrome

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October 10, 2024

Introduction

- The Applicant is seeking approval of a new molecular entity, elamipretide, for the treatment of patients, 12 years or older, with Barth Syndrome (BTHS)
- FDA is soliciting advice from the Advisory Committee on whether elamipretide is effective for the proposed indication based on the available evidence

Regulatory Standard for Effectiveness

Substantial Evidence of Effectiveness

- A drug's effectiveness must be established prior to approval based on substantial evidence[1]
- Substantial evidence generally requires at least two adequate and well-controlled (AWC) clinical investigations, each convincing on its own
- When more than one AWC investigation is not feasible/practical, FDA may consider convincing evidence from one AWC clinical investigation together with confirmatory evidence (CE) as substantial evidence[2]

[1]See the 2019 FDA draft guidance for industry, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

[2]See the 2023 FDA draft guidance for industry, Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence

Substantial Evidence of Effectiveness

- To establish effectiveness, it is essential to distinguish the effect of the drug from other influences (e.g., spontaneous change in the disease course, placebo effect, biased observation)
- This is accomplished with features of an AWC clinical investigation, which include:
  - Study design that permits a valid comparison with a control to provide a quantitative assessment of drug effect
  - Adequate measures to minimize bias and assure comparability of the study groups
  - Well-defined and reliable methods of assessing subjects' response (i.e., efficacy endpoints)
  - Analysis of study results adequate to assess the effects of the drug

Key Data to Assess Elamipretide's Efficacy in BTHS

- The clinical studies conducted to assess elamipretide's efficacy include:
  - SPIBA-201, Part 1 – a randomized, double-blind, placebo-controlled trial
  - SPIBA-201, Part 2 – a single-arm, open-label extension study
  - SPIBA-001 – an externally-controlled study
- The Applicant also cites other information as being supportive (i.e., potential confirmatory evidence), such as the nonclinical findings, biomarkers, and patient/caregiver perception of change assessments
- In this presentation, FDA will provide our assessment of these studies and data

Overview of Barth Syndrome

Barth Syndrome (BTHS)

- Rare, serious, life threatening, X-linked recessive mitochondrial disorder
- Caused by defects in the *TAFAZZIN* gene that result in cardiolipin abnormalities, leading to mitochondrial dysfunction
- Worldwide incidence: 1:300,000-1:400,000 live births
- Diagnosed by genetic testing or elevation of the monolysocardiolipin (MLCL) to tetralinoleoyl cardiolipin (CL) ratio (MLCL/CL ratio, Cardiolipin ratio)

Barth Syndrome (BTHS)

- Infantile onset cardioskeletal disease characterized by cardiomyopathy, hypotonia, growth delay, neutropenia, fatigue and exercise intolerance
- Mortality is highest in the first 4 years of life (cardiomyopathy leading cause of death); survivors improve/stabilize cardiac function in middle childhood years
- Predominant manifestations in adolescents and young adults are fatigue, poor stamina, and exercise intolerance
- Currently, no approved treatment for BTHS; represents significant unmet need

Efficacy

Data Submitted to Support Effectiveness of Elamipretide for the Treatment of Patients With BTHS

Elamipretide: Proposed Mechanism of Action (MOA)

- The Applicant proposes that elamipretide:
  - Penetrates cell membranes and transiently localizes to the inner mitochondrial membrane
  - Ameliorates the cardiolipin deficit and associated electron transport chain deficiencies, improving adenosine triphosphate in dysfunctional mitochondria, improving mitochondrial morphology, and preventing pathological formation of reactive oxygen species
- The Applicant states these effects improve cellular bioenergetics and reduce pathological apoptosis or necrosis

Elamipretide: FDA Review of MOA

FDA review of nonclinical data:

- Supports proposed MOA relating to improvement of mitochondrial function
  - Elamipretide localizes to and is enriched in the inner mitochondrial membrane, the hypothesized site of therapeutic action
  - Elamipretide improved mitochondrial morphology and function in BTHS and non-BTHS models
- Uncertain whether elamipretide might reduce apoptosis and necrosis, and improve cardiac structure and function in BTHS models
  - Reductions in apoptosis/necrosis and related sequelae only observed in models that differ in etiology from BTHS
  - No convincing data that demonstrate improved cardiac structure and function in TAZ-deficient mice

Effects of Elamipretide in Animal Models

Parameter	**BTHS Models** **(TAZ-Knockdown mice model; durations up to 10 weeks)**	**Non-BTHS Models*** **(Heart failure, ischemia-reperfusion, aged mouse models; durations up to 12 weeks)**
Mitochondrial structure	Improved	Improved
Mitochondrial function	Improved	Improved
Apoptosis/necrosis	No data	Improved
Cardiac function	No improvement	Improved
MLCL/CL ratio	No improvement	Equivocal (in aged mice)
**Tafazzin* gene is intact in non-BTHS model		

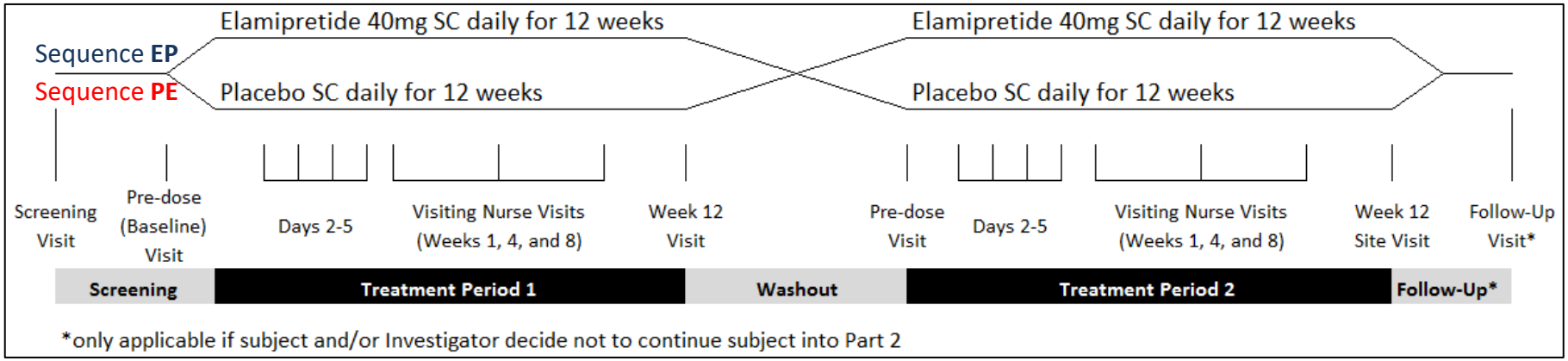
Elamipretide: Clinical Data in Diseases other than BTHS

- There are numerous published trials of elamipretide in other conditions e.g., other mitochondrial diseases, heart failure, etc.
- Some early-stage trials reported improvements, but these were not confirmed in subsequent trials, e.g.,
  - A small (N=36) phase 1/2 trial in patients with primary mitochondrial myopathy showed a significant increase in 6-minute walk distance (6MWD) compared to placebo, but a subsequent larger phase 3 trial (N=218) did not confirm these changes
  - A small cardiomyopathy trial (N=36) showed some changes in echocardiographic parameters after a high-dose infusion, but a subsequent larger phase 2 trial (N=71) did not confirm these changes

SPIBA-201, Part 1
(TAZPOWER)

SPIBA-201, Part 1

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Crossover Trial to Evaluate the Safety, Tolerability, and Efficacy of Elamipretide in Subjects with Genetically Confirmed BTHS



Source: SPIBA-201 CSR Section 9.1, Figure 1
Abbreviations: E, elamipretide; P, placebo; SC, subcutaneous
Washout was 4 weeks in duration. On days 2-5 of each period, subjects could be evaluated at the trial center daily and receive a daily injection of elamipretide for safety oversight, at the discretion of the investigator.

SPIBA-201, Part 1: Eligibility Criteria

- **Inclusion criteria**:
  - Male ≥ 12 years with genetically confirmed BTHS
  - Ambulatory, but impaired 6MWD at baseline visit (investigator discretion)
  - Stable medication regimen for 30 days before baseline visit
- **Exclusion criteria**:
  - In-patient hospitalization within 30 days prior to the baseline visit
  - Patient undergoing an apparent pubertal growth spurt
  - History of heart transplantation or awaiting a heart transplant
  - Implantable cardioverter defibrillator (ICD) discharge within the 3 months prior to baseline or expected to undergo ICD implantation during the trial

SPIBA-201, Part 1: Primary Endpoints

- Two primary endpoints:
  - Distance walked, in meters, during 6-minute walk test (6MWT)
  - Average of daily Total Fatigue Score (TFS) on Barth Syndrome Symptom Assessment (BTHS-SA) over 7 consecutive days prior to study visit
- Elamipretide compared to placebo after 12 weeks of treatment
- Used Hochberg's procedure to control family-wise Type 1 error rate at 0.05

SPIBA-201, Part 1: TFS BTHS-SA Primary Endpoint

- **BTHS-SA** is a patient-reported outcome (PRO) questionnaire that assesses symptoms of tiredness, fatigue, and muscle weakness using 8 or 9 questions depending on the version (i.e., adult or adolescent)
- Each question has 5 response categories scored 1 (not at all) to 5 (very severe)
- Applicant used **TFS** comprised of responses to the following three questions on the BTHS-SA:
  - Question 1 [tiredness at rest]
  - Question 2 [tiredness during activities]
  - Question 4 [muscle weakness during activities]
- TFS responses range from 3 (best) to 15 (worst); lower scores reflect less symptoms

SPIBA-201, Part 1: Baseline Demographics

Patient disposition : 16 subjects screened, 12 subjects treated and completed Part 1

Baseline patient characteristics: Median age: 16.5 years (range 12-35 years); 4 adults and 8 children

Characteristic	All Subjects (N=12)
Age (years), n	12
Mean (SD)	19.5 (7.6)
Median (min, max)	16.5 (12, 35)
Weight (kg), n	12
Mean (SD)	50.8 (18.9)
Median (min, max)	43.8 (31.4, 85.9)
Height (cm), n	12
Mean (SD)	167.3 (14.6)
Median (min, max)	167.1 (150.4, 187.7)

Abbreviations: cm, centimeter; kg, kilogram; max, maximum; min, minimum; SD, standard deviation.

SPIBA-201, Part 1: Primary Endpoint Results

Primary Endpoint: 6MWD (Meters)	Elamipretide N=12	Placebo N=12
Pre-dose		
Mean (SD)	400.1 (55.1)	412.6 (60.2)
End of treatment period (Primary endpoint)		
Estimated* mean (SD)	443.1 (65.4)	443.9 (77.1)
Estimated mean difference (95% CI)	-0.8 (-45.9, 44.3)	
p-value	**0.97**	

Source: SPIBA-201 CSR Section 11.4, Table 12
Abbreviations: CI, confidence interval; 6MWD, 6-minute walk distance; SE, standard error; SD, standard deviation
Pre-dose 6MWD is defined as the distance walked at baseline before the first elamipretide administration.
*Estimated - Least square mean (LSM)

SPIBA-201, Part 1: Primary Endpoint Results

6MWD (meters)	Elamipretide N=12	Placebo N=12
FDA Additional Analysis		
Change from Pre-dose at End of Treatment Period		
Estimated Mean (SE)	43.0 (13.5)	31.3 (13.5)
Estimated Mean Difference (95% CI)	11.7 (-25.8, 49.1)	
Nominal p-value	**0.50**	

Abbreviations: 6MWD, 6-minute walk distance; SE, standard error; SD, standard deviation

A mean placebo effect of approximately 30 meters was observed.

SPIBA 201, Part 1: Primary Endpoint Results

TFS ranges from 3 (best score, no tiredness/muscle weakness) to 15 (worst score)

Primary Endpoint: TFS on BTHS-SA	Elamipretide N=12	Placebo N=12
Pre-dose		
Mean (SD)	7.7 (1.94)	7.4 (1.38)
End of Treatment Period (Primary endpoint)		
Mean (SD)	6.3 (2.06)	6.2 (1.64)
Estimated Mean Difference (95% CI)	-0.1 (-0.8, 0.9)	
p-value	**0.90**	

Source: SPIBA-201 CSR Section 11.4, Table 20
Abbreviations: TFS, Total Fatigue Score; SE, standard error; SD, standard deviation
Pre-dose BTHS-SA score is defined as the score at baseline before the first elamipretide administration.

SPIBA 201, Part 1: Primary Endpoint Results

Primary Endpoint: TFS on BTHS-SA	Elamipretide N=12	Placebo N=12
FDA Additional Analysis		
Change from Pre-dose at End of Treatment Period		
Estimated Mean	-1.4	-1.2
Estimated Mean Diff (95% CI)	-0.2 (-1.2, 0.8)	
Nominal p-value	**0.70**	

Abbreviations: TFT, Total Fatigue Score; SE, standard error; SD, standard deviation
Pre-dose BTHS-SA score is defined as the score at baseline before the first elamipretide administration
On the BTHS-SA, lower scores are better. A decrease in scores is an improvement

SPIBA 201, Part 1: Secondary Endpoint Results

Secondary endpoints planned to be tested within Type 1 error control

Secondary Endpoint	Treatment	LS Mean at End of Part 1	LS Mean Change From Predose Baseline	Nominal p-value
HHD (Newtons) *(Higher scores are better)*	Elamipretide	135.9	4.7	0.65
	Placebo	129.3	6.2	
SWAY Balance Score *(Higher scores are better)*	Elamipretide	78.7	7.9	0.21
	Placebo	71.4	2.5	
5XSST (seconds) *(Shorter times are better)*	Elamipretide	14.0	1.1	0.67
	Placebo	13.7	0.1	
PGI Symptoms Scale *(Lower scores are better)*	Elamipretide	1.4	-0.3	0.43
	Placebo	1.6	-0.1	
CGI Symptoms Scale *(Lower scores are better)*	Elamipretide	1.6	-0.2	1.00
	Placebo	1.6	0.2	
PROMIS Fatigue Short Form *(Lower scores are better)*	Elamipretide	53.8	-0.4	0.75
	Placebo	53.1	-1.6	

Source: Reviewer

Abbreviations: CGI, clinician global impression; 5XSST, 5 times sit-to-stand-test; HHD, handheld dynamometry; LS, least squares; PGI, patient global impression; PROMIS, patient reported outcome measurement information system

SPIBA 201, Part 1: Exploratory Endpoint Results

Exploratory Endpoint: MLCL/CL Ratio	Elamipretide N = 12	Placebo N = 12
Pre dose		
Mean (SD)	19.8 (20.8)	19.0 (13.7)
End of Treatment Period		
LS mean	17.0	15.5
LS mean difference (95% CI)	1.5 (-6.7, 9.7)	
Nominal p-value	**0.69**	
FDA Additional Analysis		
Change from Pre-dose at End of Treatment Period		
LS Mean	-2.8	-3.4
LS Mean Diff (95% CI)	0.7 (-13.5, 14.8)	
Nominal p-value	**0.92**	

Source: SPIBA-201 CSR Section 11.4, Table 120
Abbreviations: CL, cardiolipin; LS, least squares; MLCL, monolysocardiolipin; SD, standard deviation

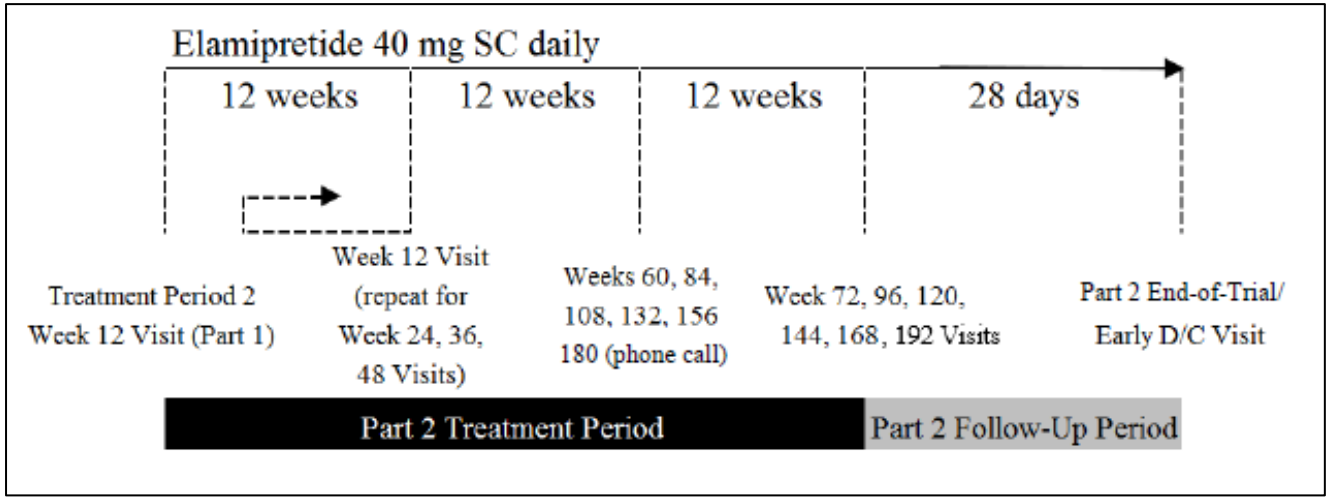
SPIBA-201, Part 1: Summary

- SPIBA-201, Part 1, an AWC trial, did not show statistically significant differences between elamipretide and placebo on its primary endpoints of 6MWT and BTHS-SA TFS
- No alpha left to test any secondary endpoints
- A mean placebo effect of ~30 meters on 6MWT was observed (placebo effect will be discussed in more detail later in this presentation)

SPIBA-201, Part 2
(TAZPOWER Extension)

SPIBA-201, Part 2

Single-arm, open-label extension of Part 1 to evaluate safety, tolerability, and longitudinal trends in efficacy of elamipretide



The first Week 12 visit in Part 2 occurred 12 weeks after the Part 1 end-of-study visit.

SPIBA-201, Part 2: Eligibility Criteria

- Inclusion criteria:
  - Subject compliant with treatment in Part 1 and appropriate to continue in Part 2, per investigator discretion
- Exclusion criteria:
  - None
- Ten of twelve subjects from Part 1 consented to participate in Part 2

SPIBA-201, Part 2: Objectives

- Primary objective: Long-term safety and tolerability of elamipretide up to 192 weeks
- Secondary objectives: Describe longitudinal trends over a treatment period of up to 192 weeks
  - Distance walked during 6MWT
  - TFS BTHS-SA
  - Mean muscle strength by handheld dynamometry (HHD)
  - Five times sit stand test (5XSST)
  - 2-dimensional (2D) and 3-dimensional (3D) echocardiographic measurements
  - Balance score from SWAY Application Balance Assessment
  - PGI Scales, CGI scales, Caregiver Global Impression (CaGI) scales
  - Biomarkers

SPIBA-201, Part 2: Subject Disposition

Subject Disposition	Subjects (N)
Enrolled in Part 2	10
Discontinued participation in Part 2 due to adverse event	2 by Week 36
Discontinued* elamipretide, but remained in Part 2	1 at Week 72
Participated in Part 2 up to and including Week 168	8
Participated in Part 2 up to and including Week 192	3

*Discontinued elamipretide because subject did not want to continue daily injections.

SPIBA-201, Part 2: Results

- While the primary endpoint was safety and tolerability, we will discuss descriptive results of the secondary efficacy endpoints
- The Applicant conducted multiple analyses such as change from baseline (pre-dose in Part 1) to Week 12, 24, 36, 48, 72, 168 for:
  - 6MWD, BTHS-SA TFS, HHD, 5XSST, SWAY Application Balance Score, PGI Symptom Scale, CGI Symptom Scale, PROMIS Fatigue T-score, MLCL/CL ratio, and other biomarkers

SPIBA-201, Part 2: PRO and Effort-Based Endpoints

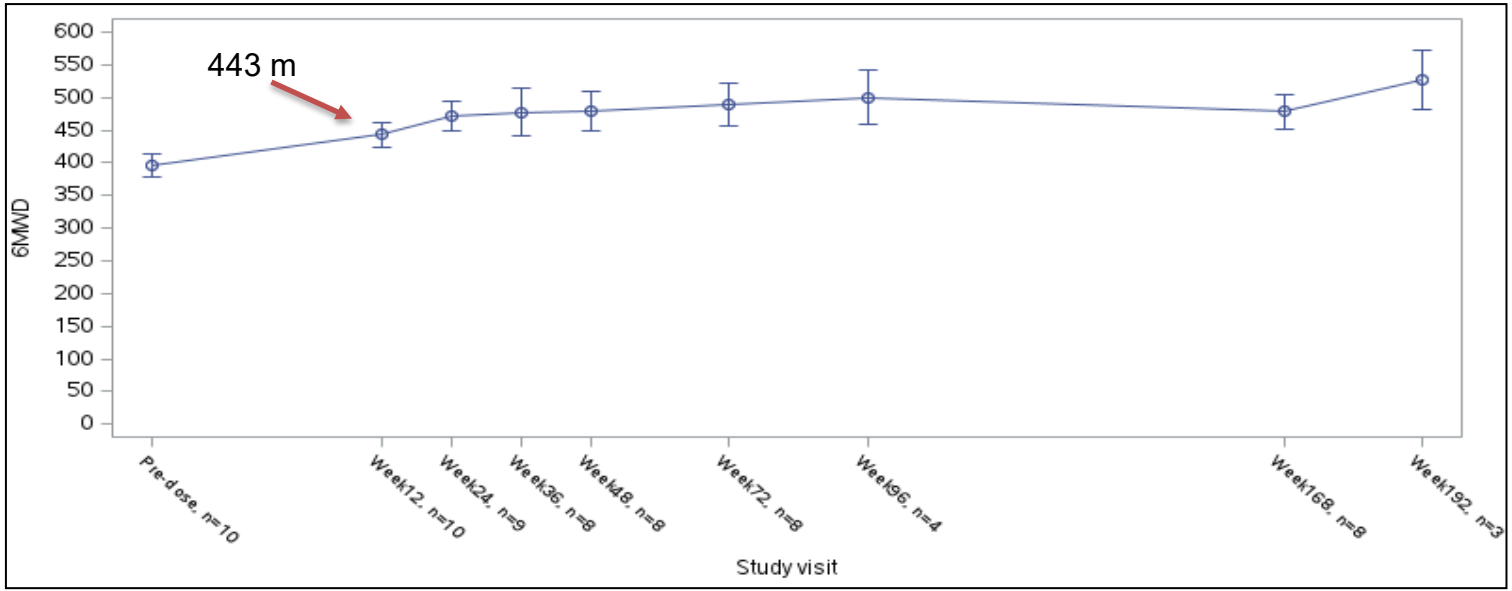
Change from Pre-dose Baseline in Part 1 to Various Timepoints in Part 2

Test	Pre-dose in Part 1 (n=10)	Change at Week 12 (n=10)	Change at Week 24 (n=9)	Change at Week 36 (n=8)	Change at Week 48 (n=8)	Change at Week 72 (n=8)	Change at Week 168 (n=8)
6-minute walk distance (meters)	382.8	60.5	91.2	95.9	97.4	106.8	96.1
BTHS-SA Total Fatigue Score (Lower scores are better)	7.7	-1.6	-0.8	-2.1	-0.6	-1.7	-1.2
HHD (Newtons) (Higher scores are better)	131.2	37.9	54.1	56.0	54.7	43.3	60.3
5XSST (seconds) (Shorter times are better)	13.0	-0.5	-1.8	-1.6	-1.8	-2.1	-2.2
SWAY Application Balance Score (Higher scores are better)	70.8	3.7	9.1	6.2	11.7	13.4	20.2

Source: Reviewer
Abbreviations: 5XSST, 5 times sit-stand-test; BTHS-SA, Barth Syndrome Symptom Assessment; HHD, handheld dynamometry; n, number of subjects.

SPIBA-201, Part 2: Effort-Based Endpoints

6MWD Mean (±SE) (meters), SPIBA-201, Part 1 Pre-dose Baseline and during SPIBA-201, Part 2



At Week 12 of Part 2, the 6MWD of 443 m is the same as the 6MWD of elamipretide-treated subjects at the end of the randomized, controlled Part 1, which was shown not to be significantly different from placebo-treated subjects.

SPIBA-201, Part 2: Effort-Dependent Endpoints

FDA Assessment:

- The open-label, single-arm design, with all subjects aware that they were receiving elamipretide, can introduce performance bias
  - The subjects knew they were receiving active treatment and might have expected they would improve
  - This could impact the extent of exerted effort
- There is no control arm to discern changes seen with elamipretide from known (e.g., extent of effort, growth and muscle development related to puberty) and unknown confounders
- The changes in the effort-based endpoints in Part 2 cannot be interpreted as a treatment effect of elamipretide in patients with BTHS

SPIBA-201, Part 2: Patient Reported Outcomes (PROs)

Patient Global Impression of Severity (PGI-S): Patients rated symptom severity experienced over the prior week on a 0-4 scale ranging from 0 (no symptoms) to 4 (very severe)

Clinician Global Impression of Severity (CGI-S): Clinicians assessed symptom severity during a visit on a 0-4 scale like PGI-S

Clinical Outcome Assessment	Pre-dose Baseline Mean (SD) (n = 10)	Week 168 Mean (SD) (n = 8)	Change from Baseline Mean (SD) 95% CI	Nominal p-value
PGI-S	1.9 (0.57)	1.1 (0.64)	-0.6 (0.74) -1.2, 0	0.05
CGI-S	1.5 (0.53)	0.4 (0.52)	-1 (0.76) -1.6, -0.4	0.01

Source: SPIBA-201 CSR Section 11 Table 39.

SPIBA-201, Part 2: PROs

- Patient/Caregiver Perception of Change video assessments:
  - Video assessments of subject/caregiver perception of change during SPIBA-201, Part 1
  - Interviews scheduled after at least 12 weeks of participation in SPIBA-201, Part 2
- Majority of the patients and caregivers reported improvements such as increased energy, stamina, muscle strength, appetite, heat tolerance, and improved wound healing. Some of the reported improvements occurred during placebo treatment period.

SPIBA-201, Part 2: PROs

FDA Assessment: Changes in PROs and Patient/Caregiver Perception of Change assessments cannot be interpreted as a treatment effect of elamipretide because:

- In Part 1, there were no statistically significant differences in the PRO measures between elamipretide and placebo
- In Part 2, there was no control group, and the open-label design could lead to biased assessment of how patients feel, knowing they were receiving elamipretide
- Patient/Caregiver Perception of Change assessments:
  - Potential for recall bias because the interviews were conducted at least 12-28 weeks after participation in Part 1
  - Unclear whether responses were impacted by subjects being unblinded in Part 2

SPIBA-201, Part 2: Cardiolipin Ratio

Change from Pre-dose Baseline in Part 1 at Different Weeks in Part 2

Biomarker	Week 12 (n=10)	Week 24 (n=10)	Week 36 (n=9)	Week 48 (n=8)	Week 72 (n=8)	Week 96 (n=8)	Week 144 (n=8)	Week 168 (n=8)
MLCL/CL_4 $(18:2)_4$	-7.8	-7	-5.6	-7.1	-16.7	-10.6	-7.2	-7.4
MLCL/CL_4 (72:8)	-5.9	-6	-5.1	-5.5	-6.3	-8.5	-6.9	-7

Abbreviations: CL, cardiolipin; MLCL, monolysocardiolipin

Pre-dose baseline in Part 1 MLCL/CL ratio was ~19; changes from pre-dose baseline are small

MLCL/CL ratio ~ 100-fold or greater in patients with BTHS versus normal controls[1]

[1] van Werkhoven MA, Thorburn DR, Gedeon AK, Pitt JJ. Monolysocardiolipin in cultured fibroblasts is a sensitive and specific marker for Barth Syndrome. J Lipid Res. 2006 Oct;47(10):2346-51

SPIBA-201, Part 2: Cardiolipin Ratio

FDA Assessment: The changes in MLCL/CL ratio in Part 2 cannot be interpreted as a treatment effect of elamipretide because:

- An elevated MLCL/CL ratio is diagnostic for BTHS, but there are no data to support a relationship of decline in MLCL/CL ratio and clinical outcomes in BTHS
- Without a control group, the changes in MLCL/CL ratio are difficult to interpret

SPIBA-201, Part 2: Summary

- SPIBA-201, Part 2 was a single-arm, open-label, uncontrolled study
- The results of various effort-based endpoints and PROs are difficult to interpret as treatment effect of elamipretide due to potential bias and lack of an adequate control

SPIBA-001

(Natural History Control Study)

SPIBA-001

SPIBA-001 was designed to generate evidence of efficacy of elamipretide because SPIBA-201, Part 1 did not find statistically significant differences, and because of limitations of SPIBA-201, Part 2

Title: A Long-Term Study to Evaluate the Efficacy of Elamipretide Compared to a Retrospective Natural History Control in Subjects with Barth Syndrome

Study design: Outcomes in SPIBA-201, Part 2 compared to an external natural history (NH) control

SPIBA-001: Study Design

Primary Endpoint: Change in 6MWD from pre-dose baseline to Weeks 64 and 76

Secondary Endpoints:

- HHD
- 5XSST
- SWAY Application Balance Assessment
- Multidomain responder index (MDRI): The MDRI used a minimally clinically important difference (MCID) responder definition for 6MWD, HHD, 5XSST and SWAY Application Balance Assessment.

SPIBA-001: Study Design

Treated Set (TRTS): Subjects from SPIBA-201, Part 1 and Part 2

Natural History Cohort (NHC): Subjects with available covariate data (age, height, 6MWD) and at least one post-baseline 6MWD

- Data collected prior to SPIBA-001 by the principal investigator for the SPIBA trials, under independent clinical research activity
- Subset of BTHS patients who attended the Interdisciplinary Clinic at Johns Hopkins' Kennedy Krieger Institute, and the BTHS Foundation International Scientific, Medical and Family Conferences held in 2014, 2016, and 2018
- This group has also been described as the "untreated set" (UNTS) or as "subjects who provided non-trial natural history data"

Propensity score methodology was used to try to balance the two study arms

SPIBA-001: Study Design

The timing and number of endpoint assessments were different between the TRTS and NHC:

- TRTS: Endpoint assessments were conducted according to schedule of assessments of SPIBA-201. For example, 6MWT was conducted at Weeks 12, 24, 36, 48, 72, 96, 120, 144, 168, and 192.
- NHC: Retrospective results of study endpoints, as and when available, were used. Some of these assessments were conducted under independent investigator-led research protocols.

Results from the TRT set and NHC were known before SPIBA-001 was designed.

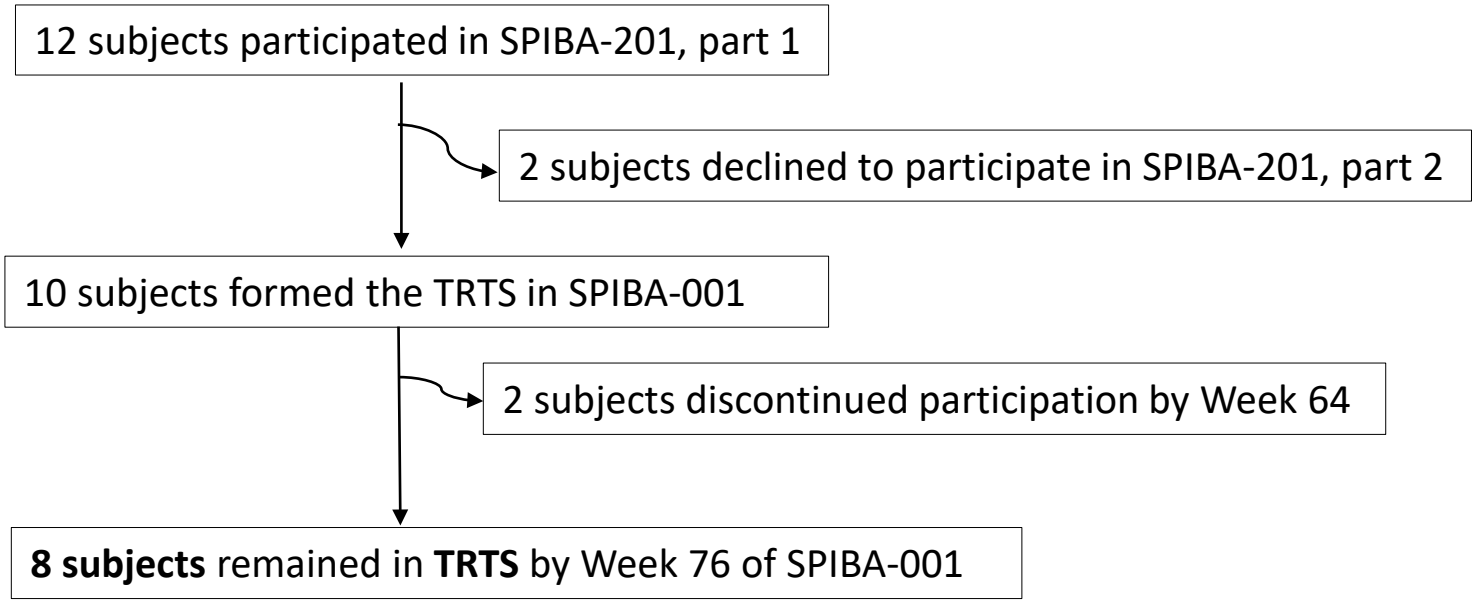
The rationale for selected timepoints of Weeks 64 and 76 to evaluate study endpoints was not provided.

SPIBA-001: Study Design

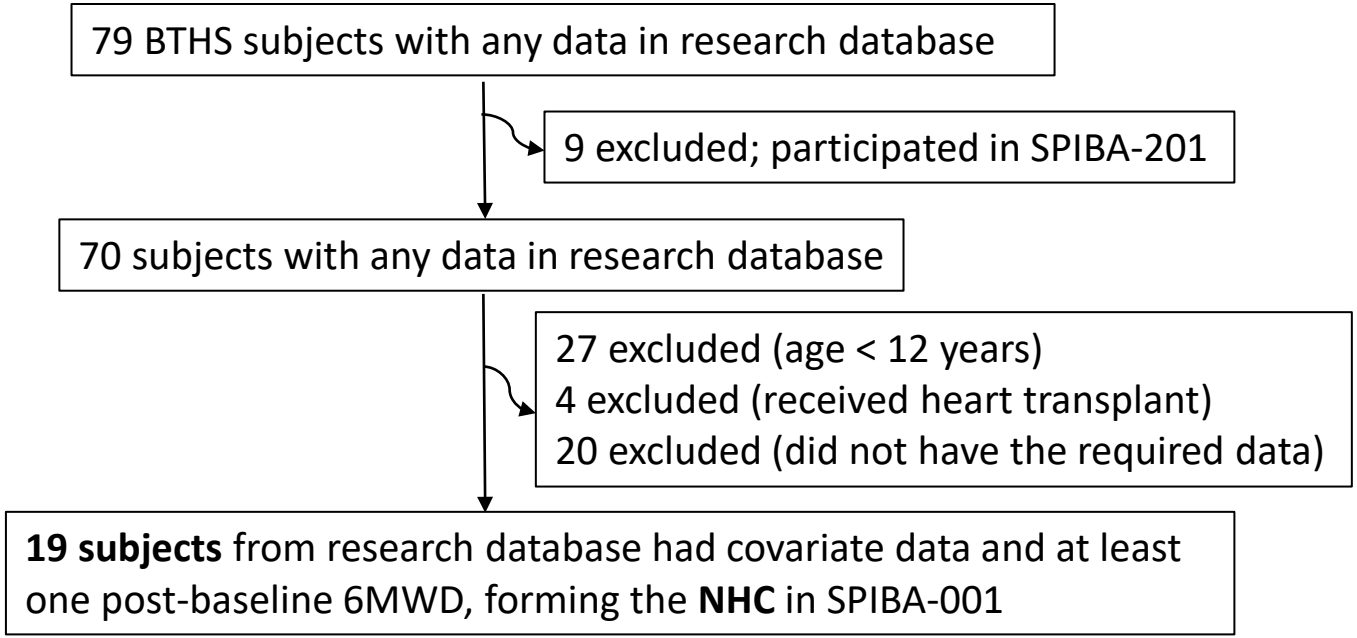
FDA Advice to Applicant (2019): FDA did not agree with the design of SPIBA-001 to evaluate treatment effect of elamipretide. The rationale for disagreement was that 6MWT:

- is effort-dependent,
- has high intra-subject variability,
- is difficult to interpret based on comparisons with an external, historical control group, especially given the negative results obtained in SPIBA-201, Part 1.

SPIBA-001: Treated Set (TRTS)



SPIBA-001: Natural History Cohort (NHC)



SPIBA-001: Results

- No subject in NHC and some subjects in TRTS had primary or secondary endpoint assessments available at Weeks 64 and 76
- Imputation was used to estimate data for primary and secondary endpoints for TRTS and NHC at Weeks 64 and 76
- Imputation is a statistical technique that replaces missing data with estimated values

SPIBA-001: Results

Using imputed endpoint values, TRTS had a larger change from baseline in 6MWD compared to NHC at Weeks 64 and 76; NHC did not show any improvement.

6MWD (meters)	Statistic	TRTS N=8	NHC N=19
Baseline	Mean	381.9	394.9
Week 64 (imputed)	Estimated mean	464.7	396.2
Change from Baseline	Estimated mean	**82.2**	**0.9**
	p-value	0.0001	
Week 76 (imputed)	Estimated mean	476.2	396.8
Change from Baseline	Estimated mean	**94.2**	**1.2**
	p-value	0.0001	

Abbreviations: 6MWD, 6-minute walk distance; TRTS, treated set; NHC, Natural History Cohort

SPIBA-001: Results

Using imputed endpoint values, TRTS had larger changes from baseline in all secondary endpoints compared to NHC, at Weeks 64 and 76.

Efficacy Assessment /Units (LS Mean Change From Baseline)	Timepoint (W = week)	TRT Set (n=8)	NH Cohort (n=19)	Nominal p-value*
HDD/Newtons Improvement=↑	Baseline	132.1	151.8	-
	W64	41.4	1.1	0.0006
	W76	48.2	2.0	0.0009
5XSST/Seconds Improvement=↓	Baseline	12.9	11.2	-
	W64	-2.2	0.0	0.052
	W76	-2.6	0.0	0.043
SWAY Balance Score Improvement=↑	Baseline	70.9	68.7	-
	W64	7.6	1.4	0.094
	W76	9.1	1.7	0.086

* Not adjusted for multiplicity

Abbreviations: LS, least squares; 5XSST, 5 times sit-to-stand; HHD, handheld dynamometer; NH, natural history; TRTS, treated set; NHC, Natural History Cohort; W, week.

SPIBA-001: Summary

FDA Assessment:

- The subjects in TRTS are the subjects from the open-label, single-arm extension, SPIBA-201, Part 2. Use of these data in an externally controlled study cannot resolve the potential bias on effort-dependent endpoints due to knowledge of treatment assignment.
- Statistical limitations of SPIBA-001 will be discussed further under Statistical Assessment.
- Hence, it is unclear if SPIBA-001 results can be interpreted as treatment effect of elamipretide.

U.S. FOOD & DRUG ADMINISTRATION

Statistical Assessment

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Office of Biostatistics
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Key Limitations of the Efficacy Data

1. Effort-dependent endpoints with knowledge of treatment (SPIBA 201, SPIBA-001)
2. Selection and confounding bias (SPIBA-001)
3. Imputed functional data (SPIBA-001)

SPIBA-201, Part 1: Primary Endpoint Results

Primary Endpoint: 6MWD (Meters)	Elamipretide N=12	Placebo N=12
Pre-dose		
Mean (SD)	400.1 (55.1)	412.6 (60.2)
End of treatment period (Primary endpoint)		
Estimated* mean (SD)	443.1 (65.4)	443.9 (77.1)
Estimated mean difference (95% CI)	-0.8 (-45.9, 44.3)	
p-value	**0.97**	

Source: SPIBA-201 CSR Section 11.4, Table 12
Abbreviations: CI, confidence interval; 6MWD, 6-minute walk distance; SE, standard error; SD, standard deviation
Pre-dose 6MWD is defined as the distance walked at baseline before the first elamipretide administration.
*Estimated - Least square mean (LSM)

Limitation #1: 6MWD Effort Dependent Endpoint

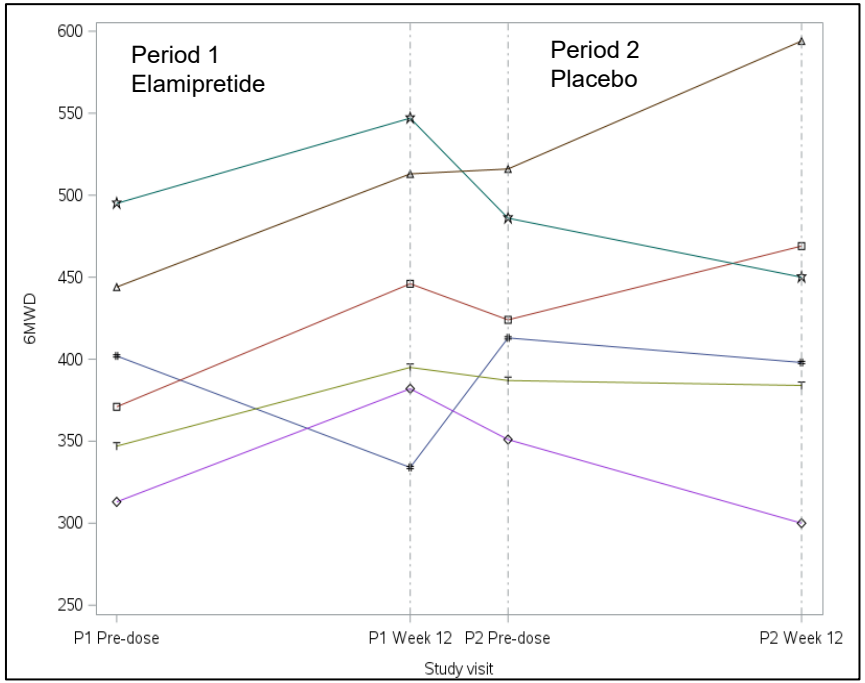
SPIBA-201, Part 1: "Placebo" Effect on 6MWD

6MWD (Mean), meters	Elamipretide/Placebo Sequence (N=6)	Placebo/Elamipretide Sequence (N=6)
Period 1 Treatment	Elamipretide	Placebo
Pre-dose	395.3	395.7
Week 12	436.2	455.3
Change from Pre-dose	40.9	**59.6**
Period 2 Treatment	Placebo	Elamipretide
Pre-dose	429.5	404.8
Week 12	432.5	450.0
Change from Pre-dose	3.0	45.2

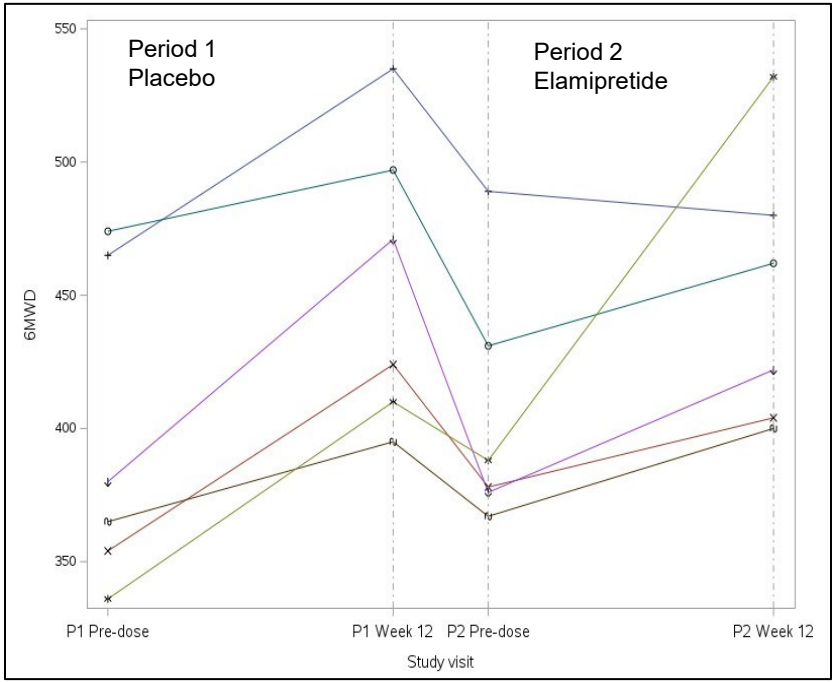
Source: Review team

Limitation #1: 6MWD Effort Dependent Endpoint

Elamipretide/Placebo Sequence



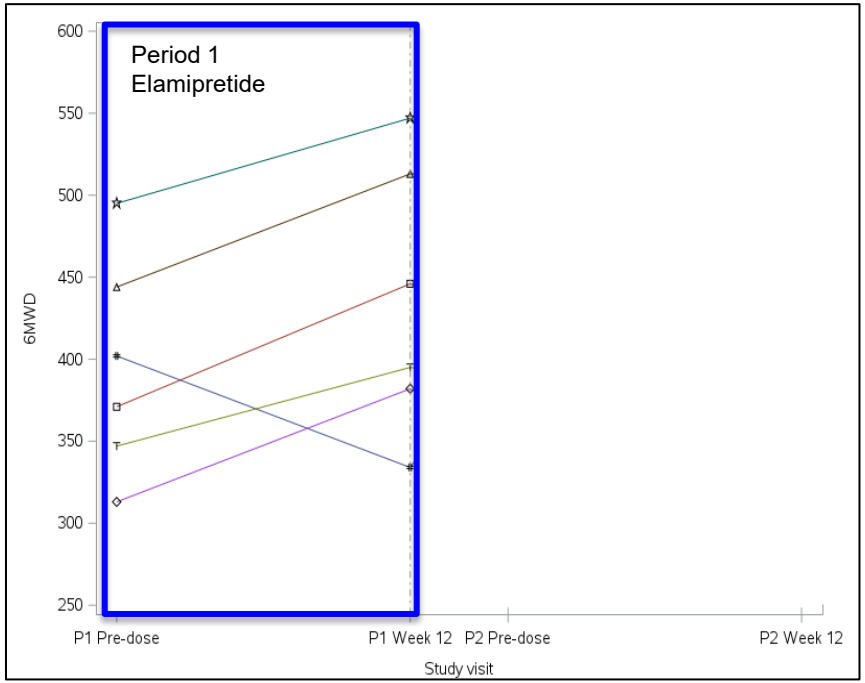
Placebo/Elamipretide Sequence



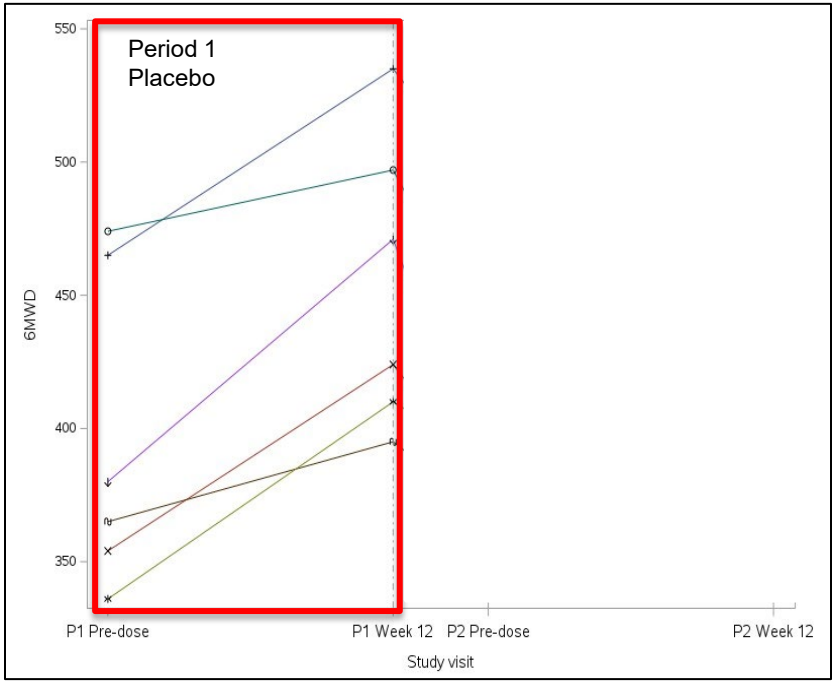
Source: Review team

Limitation #1: 6MWD Effort Dependent Endpoint

Elamipretide/Placebo Sequence



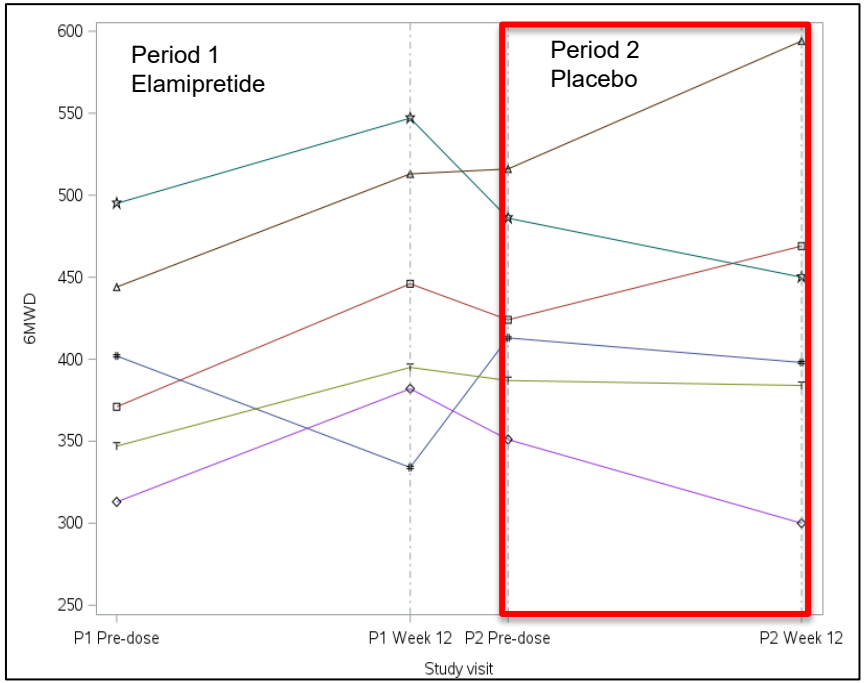
Placebo/Elamipretide Sequence



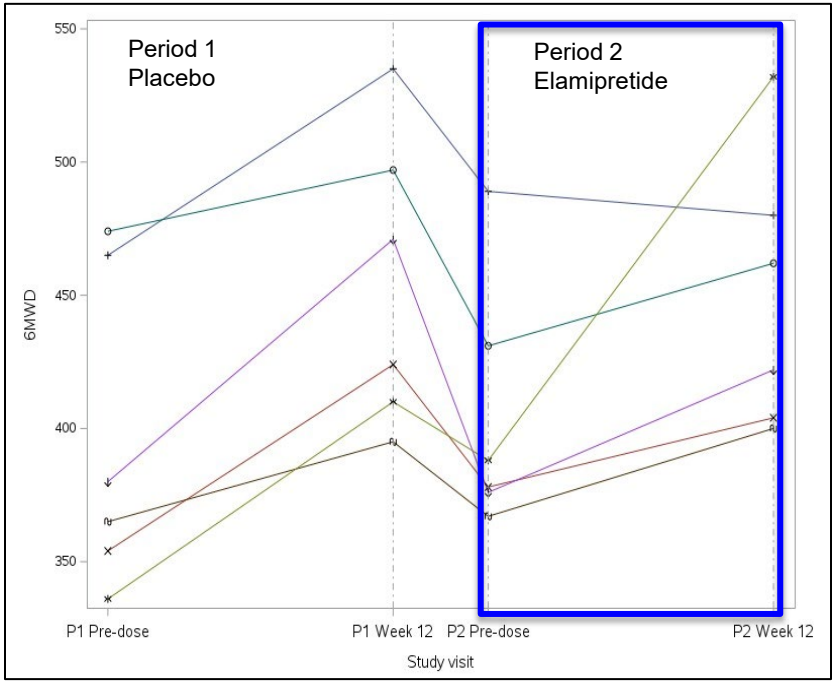
Source: Review team

Limitation #1: 6MWD Effort Dependent Endpoint

Elamipretide/Placebo Sequence



Placebo/Elamipretide Sequence



Source: Review team

Limitation #1: Effort-Dependent Endpoints

- 6MWD is an effort-dependent endpoint with high intra-subject variability
- In SPIBA-201, Part 1, a sizeable placebo effect on 6MWD was observed and no statistically significant difference between elamipretide and placebo on 6MWD was observed
- Unclear whether changes in various endpoints in SPIBA-201, Part 2 reflect a treatment effect of elamipretide in the absence of a control arm and potential performance bias in open-label assessments
- Similar concerns apply to the other effort-dependent endpoints

Limitation #2: Selection and Confounding Bias (SPIBA-001)

- **Construction of NHC in SPIBA-001:**
  - 79 patients in the NH cohort
  - 19 (24%) patients met the inclusion criteria
- **Selection Bias**: Arising from considering a subset of the NH cohort
- **Confounding Bias**: Arising from lack of treatment randomization

Limitation #2: Selection and Confounding Bias (SPIBA-001)

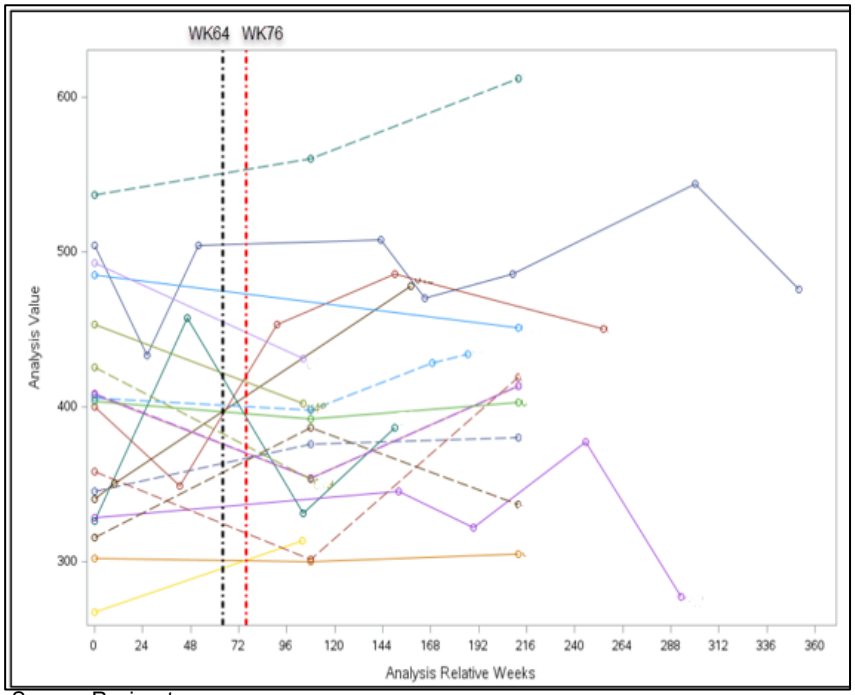
- Propensity score method in SPIBA-001 does not address the following biases inherent to the study design:
  - Impact of selection bias
  - Impact of bias from lack of blinding and effort-dependent endpoints with high intra-patient variability

Limitation #2: Selection and Confounding Bias (SPIBA-001)

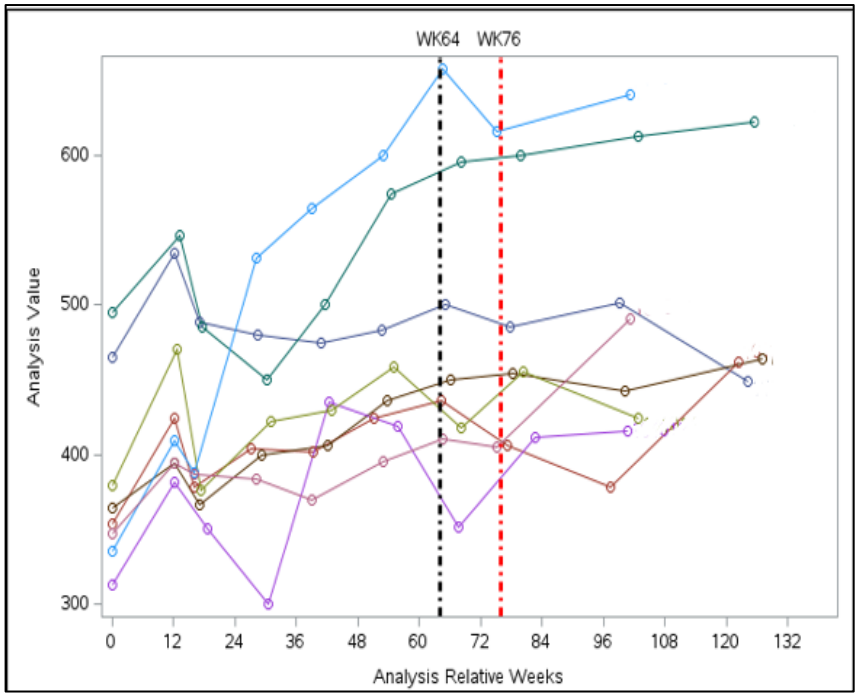
- Limitations of Propensity Score (PS) Method:
  - No pre-specification of study design and analyses
  - Limited number of covariates (age, height, baseline 6MWD) considered in the PS model
  - Limited sample size

Limitation #3: Analyses Based on 100% Imputed Data (SPIBA-001)

Actual Observed 6MWD Values in NHC Cohort



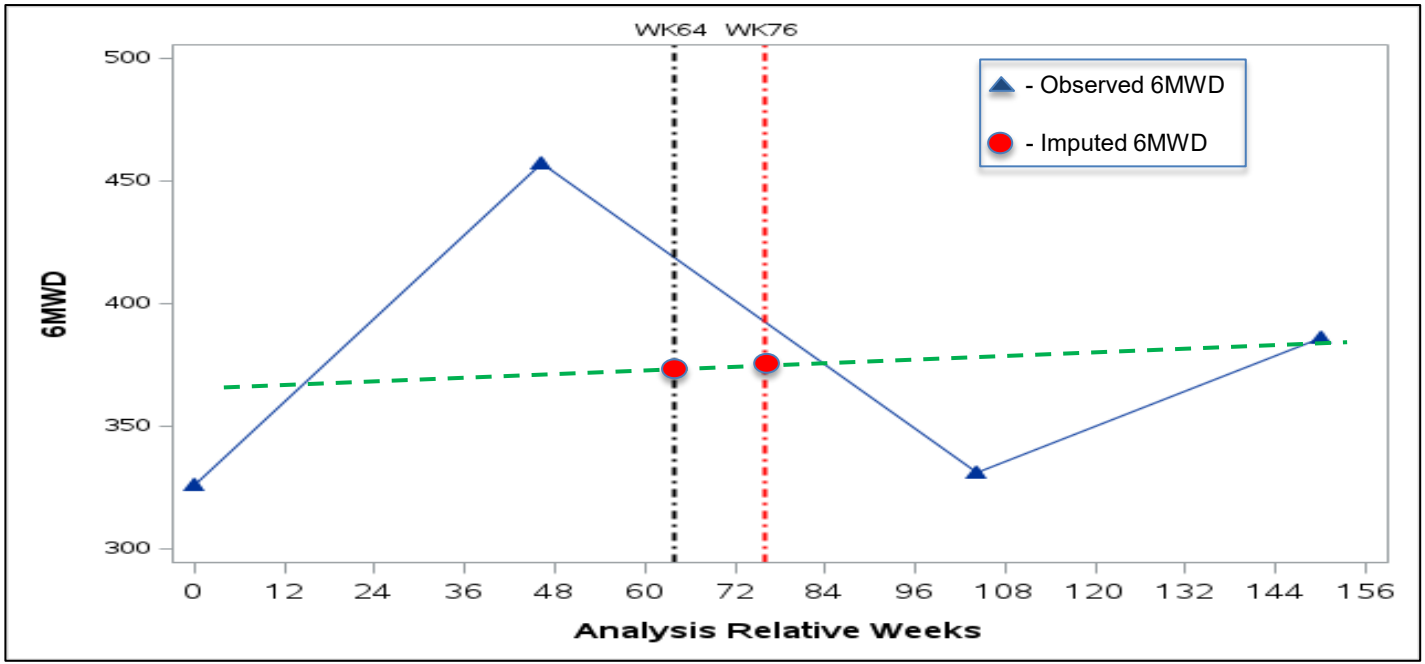
Actual Observed 6MWD Values in TRTS Set



Source: Review team

Limitation #3: Analyses Based on 100% Imputed Data (SPIBA-001)

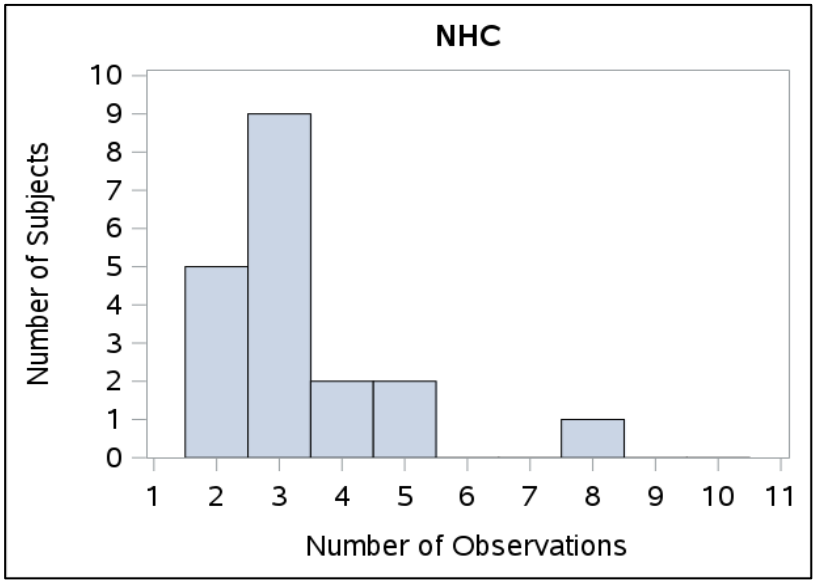
Illustration of Imputation by Regression Line

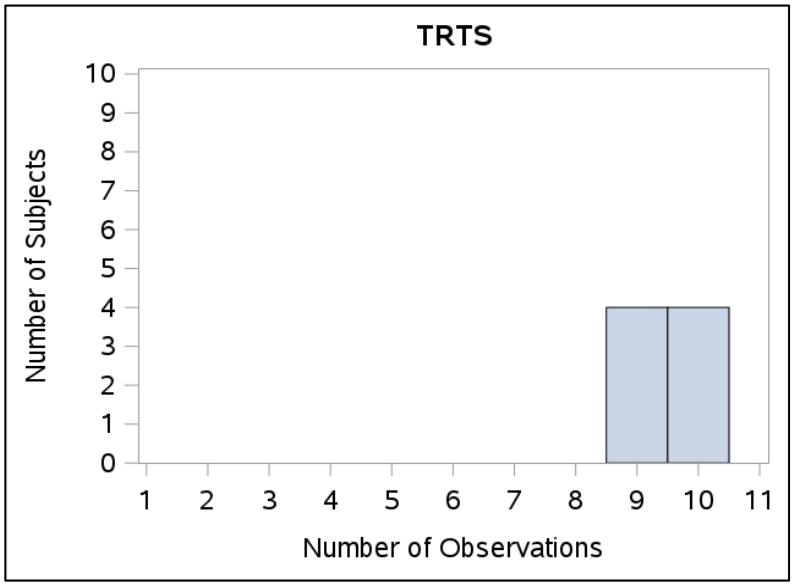


Source: Review team

Limitation #3: Analyses Based on 100% Imputed Data (SPIBA-001)

Insufficient number of available observed 6MWD





Source: Review team

Limitation #3: Analyses Based on 100% Imputed Data (SPIBA-001)

Observations should be reasonably close to the imputed timepoints

- Closest 6MWD observations before and after Week 64 (Day 448) for NHC shown in table
  - Average number of days before: 392 days
  - Average number of days after: 381 days
- TRTS had scheduled visits at Week 64
  - Average number of days from Week 64:

    15 days with a range of 2-30 days

Subject	NHC	
	# of Days Before Week 64	# of Days After Week 64
1	83	554
2	151	190
3	125	281
4	379	658
5	447	617
6	447	281
7	447	1034
8	447	307
9	447	308
10	447	307
11	447	281
12	447	279
13	447	307
14	447	308
15	447	307
16	447	308
17	447	307
18	447	307
19	447	307

Limitation #3: Analyses Based on 100% Imputed Data (SPIBA-001)

- Difficulty interpreting results based on 100% imputed data
- Reduced reliability of imputed data
  - Insufficient number of observations for imputation
  - Large gaps between the observed visits
- Problem with single imputation

Summary Assessment

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Clinical Reviewer
Division of Cardiology and Nephrology

Summary

- The primary endpoint results of SPIBA-201, Part 1, an AWC clinical investigation, do not show a treatment effect of elamipretide versus placebo.
- Due to the limitations discussed, we have concerns that SPIBA-201, Part 2 and SPIBA-001 are not AWC clinical investigations for the following endpoints, rendering it unclear whether there is a treatment effect of elamipretide on:
  - 6MWD
  - Other effort-dependent endpoints (e.g., handheld dynamometry, 5 times sit-to-stand-test)
  - Patient reported outcomes, including Total Fatigue Score BTHS-SA
  - MLCL/CL ratio
- We now turn to the echocardiography data from SPIBA-201 and SPIBA-001 to assess whether there is a treatment effect of elamipretide on the echocardiographic parameters.

SPIBA-201, Part 1: Echocardiographic Data

SPIBA-201, Part 1: Echocardiographic Data

- In SPIBA-201, Part 1, the Applicant compared 27 echocardiographic parameters between the elamipretide and placebo groups
- There were data for 12 subjects (8 children ages 12-17 years; 4 adults ages 21-35)
- Eligibility criteria for SPIBA-201, Part 1 did not require presence of cardiomyopathy at baseline
  - Nine of 12 subjects were reported as having remote history of cardiomyopathy and/or heart failure (12-35 years before enrollment)
  - Mean values of the echocardiographic parameters that characterize left ventricular (LV) structure and function were normal at baseline in all patients

SPIBA-201, Part 1: Echocardiographic Data

At baseline, key echocardiographic measures of LV structure and function were normal

Echocardiographic Measurement	Baseline Value (Mean ± SD)	Normal Reference Range (2 SD)
Mean LV ejection fraction (LVEF) (%)	63.9 (5.6)	52 – 72
Mean LV posterior wall thickness in diastole (cm)	0.8 (0.15)	0.6 – 1.0
Mean LV EDV indexed to BSA (mL/m^2)	44.4 (10.5)	34 – 74
Mean LV global longitudinal strain (%)	-19.7 (1.9)	-16.8 ± 2
Mean LV mass indexed to BSA (g/m^2)	84.3 (17.9)	50 – 102
Left atrial volume (LAV) indexed to BSA (ml/m^2)	27.6 (5.9)	16 – 34

Abbreviations: BSA, body surface area; LV, left ventricular; LVEDV, left ventricular end diastolic volume, SD standard deviation

SPIBA-201, Part 1: Echocardiographic Data Results

At end of the randomized treatment period (12 weeks), there was no significant between-group difference in change from baseline in echocardiographic measures of LV structure and function

Echocardiographic Parameter	Elamipretide (N=12)		Placebo (N=12)		LSM Difference (95% CI)	Nominal p-value
	Baseline Mean (SD)	Week 12 Mean (SD)	Baseline Mean (SD)	Week 12 Mean (SD)		
2D Echocardiographic measurements						
LVEF (%)	63.9 (5.6)	62.0 (4.6)	62.7 (3.3)	64.1 (4.5)	-2.1 (-5.6, 1.4)	0.21
LVEDV/baseline BSA (mL/m^2)	44.4 (10.5)	48.4 (12.5)	46.4 (9.4)	49.6 (12.3)	-1.1 (-8.9, 6.6)	0.75
LV global longitudinal strain (%)	-19.7 (1.9)	-20.2 (1.4)	-20.0 (2.0)	-20.3 (1.9)	0.1 (-1.1, 1.4)	0.81
LAV/baseline BSA (mL/m^2)	27.6 (5.9)	28.3 (5.6)	27.7 (8.0)	27.4 (6.6)	0.9 (-2.3, 4.1)	0.54
LV mass/baseline BSA (g/m^2)	84.3 (17.9)	83.5 (18.0)	89.6 (12.7)	88.1(21.2)	-4.5 (-21.8, 12.7)	0.57
Lateral MV annulus e' (cm/s)	20 (0.0)	20 (0.0)	20(0.0)	20 (0.0)	0.0 (-1, 2)	0.62

Abbreviations: BSA, body surface area; LVEDi, left ventricular end diastolic volume; LV EF, left ventricular ejection; LAV, left atrial volume.

SPIBA-201, Part 1: Echocardiographic Data Summary

These echocardiographic data do not show a treatment effect of elamipretide on cardiac structure or function after 12 weeks of treatment.

SPIBA-201, Part 2: Echocardiographic Data

SPIBA-201, Part 2: Echocardiographic Data

- 10 subjects: 7 children ages 12-17 years; 3 adults ages 21-35 years
- Echocardiographic data obtained at Weeks 12, 24, 36, 48, 72, 96, 168, 192
- Applicant evaluated change from baseline in multiple echocardiographic parameters at multiple timepoints and proposed that an increase in left ventricular stroke volume indexed to body surface area (LVSVi) suggests a treatment effect of elamipretide
- Hence, we discuss changes in LV volumes (LV end diastolic volume, LV end systolic volume and LV stroke volume) and LV ejection fraction (LVEF)

SPIBA-201, Part 2: Echocardiographic Data

- LV End Diastolic Volume (LVEDV): Volume of blood in LV at end of diastole
- LV End Systolic Volume (LVESV): Volume of blood remaining in LV at end of systole
- LV Stroke Volume (LVSV): Volume of blood pumped out of the LV during systole

$$LVSV = LVEDV - LVESV$$

- LV Ejection Fraction (LVEF): Percentage of blood ejected during systole in relation to EDV

$$LVEF = \left[\frac{LVEDV - LVESV}{LVEDV}\right] * 100$$

- Indexing to Body Surface Area (BSA): Performed to standardize measurements across patients with different body sizes, which improves accuracy of measurements

SPIBA-201, Part 2: Echocardiographic Data Results

Mean LV volumes indexed to concurrent BSA, and LVEF (by 3D echocardiography) remained generally within the normal range at various timepoints in SPIBA-201, Part 2

Echocardiographic parameter (3D) Mean	Normal Range in adults	Week 12 (n = 10)	Week 24 (n = 9)	Week 36 (n = 8)	Week 48 (n = 8)	Week 72 (n = 8)	Week 96 (n = 4)	Week 168 (n = 8)	Week 192 (n = 3)
LVEDVi (mL/m^2)	41-85	51.5 (6.5)	50.8 (7.8)	54.8 (12.9)	54.3 (8.2)	52.4 (7.8)	54 (8.4)	66.6 (14.1)	59.8 (8.8)
LVESVi (mL/m^2)	14-24	20.1 (3.5)	20.2 (3.4)	21.3 (5.8)	21.2 (3.8)	20.6 (2.9)	20.7 (3.0)	26.2 (6.)	23.7 (4.6)
LVSVi (mL/m^2)	35.6-53	31.4 (3.6)	30.6 (5.4)	33.4 (7.5)	33.1 (4.8)	31.9 (5.9)	33.3 (6.0)	40.4 (8.8)	36.1 (5.9)
LV EF (%)	54-70	60.6 (4.2)	61.1 (3.1)	60.1 (3.5)	61.2 (2.7)	60.6 (4.2)	61.4 (3.1)	61.3 (3.9)	60.4 (4.6)

Abbreviations: BSA, body surface area; i, indexed to concurrent BSA; LVEDi, left ventricular end diastolic volume; LVESVi, left ventricular end systolic volume, LVSVi, left ventricular stroke volume; LV EF, left ventricular ejection fraction.

SPIBA-201, Part 2: Echocardiographic Data Results

Echocardiographic parameter (3D) Mean	Normal Range in Adults	Pre-dose baseline Mean (SD)	Week 168 Mean (SD)
LVEDVi (mL/m^2)	41-85	46.1 (8.5)	66.6 (14.1)
LVESVi (mL/m^2)	14-24	18.1 (3.2)	26.2 (6.0)
LVSVi (mL/m^2)	35.6-53	28.0 (6.2)	40.4 (8.8)
LV EF %	54-70	60.6 (4.2)	61.3 (3.9)

Abbreviations: BSA, body surface area; i, indexed; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; LVSV, left ventricular stroke volume; LV EF, left ventricular ejection fraction; SD standard deviation.

- LVSV is a hemodynamic parameter determined by LV contractility, preload, and afterload. Hence, cardiac and extracardiac factors (e.g., blood volume, cardiac function, vascular tone) can influence LVSV.
- With the unchanged LV EF and the small change in LVESV compared to LVEDV, the LVSV increase is likely driven by increases in LVEDV. Other hemodynamic factors that may impact LVSV were not reported.

SPIBA-201, Part 2: Echocardiographic Data Summary

- Depending on the reference used, some baseline LVSVi and LVEDV values were lower than the reference range. However, at baseline, several echocardiographic parameters used to evaluate or associated with diastolic dysfunction were normal (e.g., diastolic mitral annular tissue velocity, left atrial volume, mean LV wall thickness, LV mass, LV global longitudinal strain). Hence, baseline echocardiographic data do not support presence of diastolic dysfunction at baseline.
- LVEDV increases up to 3-fold during normal childhood and would be expected to increase over time in children enrolled in SPIBA-201, Part 2. Without a control arm, the increase in LVEDV, and therefore LVSVi, cannot be interpreted as a treatment effect of elamipretide.

Post Hoc Echocardiographic Data Analysis

Post Hoc Echocardiographic Data Analysis

- The Applicant conducted post hoc analysis comparing LVEDV, LVESV and LVSV between patients who received elamipretide in SPIBA-201 and patients with BTHS who had echocardiographic data available from at least 1 timepoint (Echo NHC) in the research database used for the NHC in SPIBA-001

- The Echo NHC subjects (n = 12; 8 subjects < 12 years) were different from the NHC in SPIBA-001 (n = 19, all subjects ≥ 12 years); only 4 patients overlapped

Post Hoc Echocardiographic Data Analysis

SPIBA-201, Part 2 and Echo NHC are not comparable with respect to several variables.

Cohort	Timing of Echocardiographic Measurements	Number of Echocardiographic Measurements	Echocardiographic Modality Used for Analysis	Age of Patients (Years)	Baseline Cardiomyopathy Phenotype
SPIBA-201 Part 2 (n = 12)	According to study protocol, consistent among patients	Median number of measurements = 10 (range, 6 to 14)	3-dimensional (D) imaging	Mean = 20 Median = 17 Range = 12 to 35	Reported history of cardiomyopathy, but normal baseline echocardiographic measurements
Echo NHC (n = 12)	No prespecified schedule	Median number of measurements = 2 (range, 2 to 5)	2D and 3D imaging were combined	Mean = 12 Median = 8 Range = 1 to 27	No information available
Relevance	Clinical indication for obtaining echocardiograms not specified	Incomplete understanding of cardiac course of Echo NHC patients	3D imaging is more accurate for LV volume measurements	Age-related changes in LV volumes makes comparing mean values inappropriate	Comparing LV volumes between different cardiac phenotypes is uninterpretable

Post Hoc Echocardiography Data Analysis Results

The Applicant conducted Mixed Model Repeated Measures Analysis to compare LV volumes between the TRTS and Echo NHC

Echocardiographic Measurement	TRTS (N =12)		Echo NHC (N = 12)		LSM Difference (95% CI)	Nominal p-value
	Baseline Mean (SD)	Post-baseline Mean (SD)	Baseline Mean (SD)	Post-baseline Mean (SD)		
LVEDVi (mL/m^2)	46.1 (8.5)	48.2 (6.9)	54.4 (18.5)	53.5 (13)	4.8 (-2.7, 12.11)	0.2
LVESVi (mL/m^2)	18.1 (3.2)	18.7 (2.9)	28.3 (16.1)	28.8 (13)	-0.8 (-7.1, 5.6)	0.8
LVSVi (mL/m^2)	28 (6.4)	29.5 (4.2)	26.1 (4.5)	24.7 (6.2)	6.7 (2.8, 10.7)	0.002

- No significant difference in change from baseline in LVEDVi or LVESVi in the TRTS vs. Echo NHC
- Nominal increase in LVSVi in the TRTS vs. nominal decline in LVSVi in the Echo NHC

Post Hoc Echocardiographic Data Analysis: Summary

Given the major limitations of the post-hoc SPIBA-201, Part 2 and Echo NHC comparison of echocardiographic parameters, the reported differences in LV volumes by the Applicant cannot be reliably interpreted as a treatment effect of elamipretide.

The relationship of changes in LV volumes with clinical outcomes is not known.

FDA Overall Efficacy Summary

Overall FDA Summary of Efficacy Findings

- FDA recognizes that Barth syndrome is a rare, serious condition without approved therapy and has significant unmet need.
- The randomized, double-blind study (SPIBA-201, Part 1) did not show statistically significant differences between elamipretide and placebo on its primary and secondary endpoints.
- FDA has difficulty attributing the findings from the single-arm, open-label extension study (SPIBA-201, Part 2) and the externally-controlled study (SPIBA-001) to elamipretide because of significant limitations discussed today.


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Charge to the Advisory Committee

Hylton V. Joffe, MD, MMSc
Director
Office of Cardiology, Hematology, Endocrinology and Nephrology
Office of New Drugs | Center for Drug Evaluation and Research | FDA

Charge to the Advisory Committee

- We are asking you to discuss whether the evidence supports a conclusion that elamipretide is effective, considering results from SPIBA 201, Part 2 and SPIBA-001 and the Applicant's other proposed supportive data
- After completing the three discussion questions, we are asking you to vote on the following:

  Based on available evidence, do you conclude that elamipretide is effective for the treatment of Barth syndrome?

Charge to Advisory Committee
Four Important Considerations

1. Your role is to consider the assessments, conclusions and perspectives from both the Applicant and FDA and then provide FDA with independent, expert advice and recommendations
2. Focus your discussion on effectiveness, specifically whether the evidence supports a conclusion that elamipretide is effective in the treatment of patients with Barth syndrome
3. We seek robust, thorough discussion of the 3 discussion questions
4. The rationale for your vote is more important than the vote itself; provide detailed rationale for your vote


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Back-up Slides

Effect of Growth on 6MWT

Subject ID	Part 1 Baseline Age (years)	Part 1 Baseline Height (cm)	Percentile	Part 2 Week 168 Age (years)	Part 2 Week 72 Height (cm)	Percentile
1	17	177.2	60.3	20	179.1	69.9
2	16	150.4	0.2	19	Discontinued	
3	17	180	74.2	20	185	91.3
4	13	152	28.8	16	Discontinued	
5	12	154.4	75.2	15	162.9	18.4
6	16	161.5	5.9	19	168	11.5
7	14	152.5	7.9	17	170.5	25.5
8	14	153.3	9.3	17	165.2	8.5

SPIBA-201 Power and Sample Size Assumptions

A sample size of approximately 12 subjects is planned. Assuming an underlying standard deviation of paired differences of 50 meters for the 6MWT distance and 1.3 points for the Total Fatigue Score on the BTHS-SA, 12 subjects provides for nearly 80% power to detect a mean improvement of 50 meters in the 6MWT or 1.3 points for the Total Fatigue Score on the BTHS-SA, with each potentially tested at the 0.025 (two-sided) level of significance (associated with a potential adjustment via Hochberg's procedure), in Part 1. Subject numbers are restricted by feasibility considerations (availability of subjects) but that recruitment could be greater if subjects are available (up to 16 subjects).