Introduction: Tafamidis

Clare Kahn, PhD
Vice President Worldwide Regulatory Strategy, Specialty Care, Pfizer Inc

Peripheral and Central Nervous System Drugs Advisory Committee

May 24, 2012
FDA White Oak Campus
Silver Spring, MD
Tafamidis - proposed trade name Vyndaqel®

Proposed Indication: for the treatment of transthyretin amyloidosis in adult patients with symptomatic polyneuropathy to delay neurologic impairment
Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP)

- Transthyretin is synthesized primarily in the liver

- Tertiary **transport** protein for **thyroxine** and **retinol** binding complex

- Transthyretin Familial Amyloid Polyneuropathy, or TTR-FAP, is one of two major phenotypes of familial amyloidoses. The other is Transthyretin Familial Amyloid Cardiomyopathy, or TTR-FAC, which is the subject of a separate development program.
TTR Instability and Amyloid Cascade are Key Features of TTR-FAP

- TTR-FAP: rare and fatal autosomal dominant genetic disease
  - Prevalence <10,000 patients worldwide
- TTR protein instability is rate-limiting step
- Amyloid cascade
- Develops into an irreversible and progressive neurodegenerative disease
- No pharmacologic treatment in US
Tafamidis MOA Blocks Amyloid Cascade

Genetic Mutation

Unstable Transthyretin Tetramer Protein

Toxic Intermediates and Amyloid

Polyneuropathy

Motor  Sensory  Autonomic

Rate-limiting Step

Tafamidis designed to bind at thyroxine binding site to stabilize tetramer and block amyloid cascade
Tafamidis: Bench to Bedside Drug Development

- Unmet Medical Need: TTR-FAP
- Clinical Observation by Treating Physician
- Laboratory Designed Drug
- Clinical Program: Fx-005, 006, 201, 303
- Patient Access
First approval in European Union

- Tafamidis (Vyndaqel) approved November 2011 under the provision of “Exceptional Circumstances”

*Vyndaqel is indicated for the treatment of transthyretin amyloidosis in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment*

- Primary post-approval commitment to follow non V30M variants via the Transthyretin Amyloidosis Outcomes Survey (THAOS) disease registry

- THAOS: only prospective disease registry for all patients with TTR amyloidosis
Considerations for Development of Tafamidis

- Rarity of patients in US and worldwide
- No precedent clinical trials for TTR-FAP
- Primary and secondary endpoints selected as suitable and feasible indicators of disease progression in TTR-FAP:
  - Endpoints validated for diabetic neuropathy
  - “Fit-for-purpose” for TTR-FAP
- Ambulation or mortality outcomes require years of treatment and exclusion of liver transplantation
## Endpoints for Replication of Efficacy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Benefits Measured by Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Co-Primaries</strong></td>
<td></td>
</tr>
<tr>
<td>Neuropathy Impairment Score-LL (NIS-LL)</td>
<td>Clinical benefit</td>
</tr>
<tr>
<td>&amp; Norfolk Quality of Life Questionnaire</td>
<td></td>
</tr>
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<td></td>
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<td>NIS-LL and subscales (motor, sensory, reflex)</td>
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<td>Measures of disease progression – likely to predict clinical benefit</td>
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<tr>
<td><strong>Modified BMI</strong></td>
<td>Measure of overall disease severity with prognostic value in TTR-FAP – likely to predict clinical benefit in this setting of TTR-FAP</td>
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<td><strong>TTR Stabilization</strong></td>
<td>Blocks rate-limiting step in disease – biologically plausible marker</td>
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Core Clinical Program

Fx-005 (V30M)
18 m, Double Blind Placebo

Fx-006
12 m, Open-label Extension

Fx-303
36 m, Ongoing Open-label Extension

Fx-201 (nonV30M)
12 m, Open-label

Replication of Efficacy Across Endpoints
Core Clinical Program

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Replication of Efficacy Across Endpoints

Confirmatory Evidence
Core Clinical Program

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Replication of Efficacy Across Endpoints

Confirmatory Evidence

Generalizability Across Variants
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Replication of Efficacy Across Endpoints
Confirmatory Evidence
Durability of Clinical Effect
Generalizability Across Variants
First prospective interventional drug development program in TTR-FAP

- Single pivotal & confirmatory evidence

Totality of the efficacy data and safety profile affords a conclusion of positive Benefit:Risk

Approval is sought to allow TTR-FAP patients earliest access to needed therapy

Commitment to further study post-approval regardless of approval pathway
### External Expert

| W. David Lewis, MD | Associate Professor of Surgery, Tufts University; Lahey Clinic Burlington, Massachusetts |
Presentation Agenda

Disease Background and Treatment Paradigm

**Steven R. Zeldenrust, MD PhD**
Assistant Professor of Medicine
Mayo Clinic, Rochester, MN

Tafamidis MOA and Clinical Pharmacology

**Jeffery W. Kelly, PhD**
Lita Annenberg Hazen Professor of Chemistry
Chairman of Molecular and Experimental Medicine
The Scripps Research Institute, La Jolla, CA

Clinical Endpoints in TTR-FAP

**Roy Freeman, MD**
Professor of Neurology
Director, Center for Autonomic & Peripheral Nerve Disorders
Harvard Medical School, Boston, MA

Tafamidis Efficacy and Safety

**Donna Grogan, MD**
Medical Consultant; Former Chief Medical Officer, FoldRx, a wholly owned subsidiary of Pfizer Inc

TTR-FAP Clinical Perspective

**Teresa Coelho, MD**
Largo Prof. Abel Salazar
Hospital Geral de Santo Antonio Hospital, Porto, Portugal

Tafamidis Benefit:Risk Assessment

**Ilise Lombardo, MD**
Medicines Development Group Lead, Tafamidis, Pfizer Inc
TTR-FAP Disease Background and Treatment Paradigm

Steven R. Zeldenrust, M.D., PhD.
Assistant Professor of Medicine
Mayo Clinic
Rochester, MN

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida
TTR-FAP Disease Background and Treatment Paradigm

Steven R. Zeldenrust, M.D., PhD.
Assistant Professor of Medicine
Mayo Clinic
Rochester, MN
TTR-FAP is a Rare, Life-Threatening Disease

- Most common form of hereditary amyloidosis worldwide
- Transmitted as autosomal dominant trait with variable penetrance
- >100 amyloidogenic mutations in TTR identified to date
- Regardless of mutation, disease pathogenesis is the same
Variability in Geographic Distribution and Genotype

- Prevalence
  - US: < 2,500
  - Worldwide: 5,000 – 10,000
- TTR-FAP is endemic in some areas, but typically sporadic worldwide
- V30M
  - Most frequent mutation worldwide
  - Endemic in Portugal, Japan, and Sweden
  - Accounts for 40% of US TTR-FAP patients
- Age at onset: 30s – 40s
- Life expectancy: 10-15 years post-onset

Ando 2005
TTR-FAP Neuropathic Disease Progression

- Length dependent axonal degeneration
  - Sensory
    - Injuries
    - Impaired ADLs
  - Motor
    - Difficulty ambulating
    - Bed or wheelchair bound

- Autonomic
  - Impotence
  - Orthostatic hypotension
  - Dysmotility
  - Urinary retention
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  - Dysmotility
  - Urinary retention
TTR-FAP is a Systemic Disease

• Cardiac
  – Conduction abnormalities
  – Cardiomyopathy

• Other
  – Renal
  – Ophthalmic
  – Meningeal
Disease Progression Due to Autonomic Dysfunction Can Lead to Severe Malnutrition and Cachexia

- Fecal incontinence, gastroparesis, and alternating bouts of constipation and diarrhea
- Unintentional weight loss

Pre-symptomatic (320 pounds)

Symptomatic (170 pounds)
Liver Transplantation

- Currently **only** accepted therapy to treat TTR-FAP
  - Halts progression of disease in majority of V30M patients
  - Long-term survival advantage
  - Significant morbidity/mortality
  - Life-long immunosuppression
  - Variable outcome in non-V30M mutations
- Waiting time for liver transplant up to a year or more
- Significant cardiac involvement necessitates combined heart/liver transplant
Liver Transplantation

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Symptomatic Treatment Options

- Symptomatic treatment for individual signs/symptoms
  - Neuropathic pain
  - Orthostatic hypotension
  - Diarrhea/constipation/gastroparesis
  - Cardiac conduction disturbances
Unanswered Questions

- What about patients with advanced disease?
- Does tafamidis have a beneficial effect for cardiac involvement?
- Will patients benefit post-liver transplant?
Unanswered Questions

• What about patients with advanced disease?
• Does tafamidis have a beneficial effect for cardiac involvement?
• Will patients benefit post-liver transplant?
Significant Unmet Medical Need Exists for TTR-FAP

• TTR-FAP is a rare, progressive, life-threatening disease which is challenging to diagnose and treat

• Liver transplantation is associated with morbidity/mortality and of variable benefit

• Other treatment options are aimed at symptomatic relief but do not affect underlying pathology

• Treatments that alter disease pathogenesis are desperately needed
Tafamidis Mechanism of Action and Dose Selection

Jeffery W. Kelly, PhD
Lita Annenberg Hazen Professor of Chemistry
Chairman of Molecular and Experimental Medicine
The Scripps Research Institute
Outline of Today’s Talk

- Provide an introduction to the transthyretin amyloid from the perspective of protein structure
- Introduce the kinetic stabilization strategy to prevent amyloidogenesis
- Experimental dose selection (20 mg once a day)
Transthyretin (TTR) Aggregation Leads to the Demise of Post-mitotic Tissue
Transthyretin—Prominent Plasma Protein Retinol Binding Protein Carrier

127AA β-sheet rich 55 kDa homotetramer

TTR-(RBP)$_2$
Human Transthyretin is a Backup Thyroid Carrier

<1% of TTR bound to $T_4$
Rate Limiting Tetramer Dissociation & Monomer Misfolding Leads to Aggregation

Functional forms of TTR

Tetramer kinetically stabilized by tafamidis  Free tetramer

Folded monomer

Folded dimers

Amorphous Oligomers  Spherical Oligomers

Fibrils  Misfolded amyloidogenic monomer

Neuropathology
All TTR Disease Variants Are Destabilized

Pathological mutations destabilize the tetramer leading to higher concentration of the amyloidogenic monomer

V30M TTR-FAP highly penetrant in Portugal

Families with V30M mutation exhibit a benign course of TTR-FAP

These individuals have a second mutation, T119M, on their second allele

Hence their heterotetramers comprising T119M and V30M subunits appear to be less amyloidogenic – Interallelic trans-suppression
A T119M/V30M Compound Heterozygous Family Reveals That Interallelic Trans–Suppression Ameliorates Pathology

Native State Kinetic Stabilization Mediated by Activation Barrier Tuning with Small Molecules

Ampholidicogenic monomer

$\Delta G^+_{T119M-TTR}$ homotetramer

$\Delta G^+_{WT}$ homotetramer

Folded monomer

Aggregation

Transition state

$\text{T-I\textsubscript{2}}$

$\text{T-I}$

$\text{Tetramer}$

Folded Monomer

Unfolded Monomer

Activation Free Energy

Tafamidis Was Designed Using a Structure-Based Approach Does Not Share Structural Features With Thyroxine

Thyroxine

Tafamidis $K_{d1} = 2 \text{ nM}$; $K_{d2} = 154 \text{ nM}$
Demonstrating Transthyretin Tetramer Stabilization & Amyloid Inhibition at 20 mg Once a Day

- Dose selection based on PK/PD
- At 20 mg steady state:
  - Plasma concentration over 1000x > Kd
  - $C_{\text{min}} = 5.2 \text{ uM}; \ C_{\text{max}} = 8.4 \text{ uM}$
  - 36 of 37 variants stabilized at the 20 mg dose

Single and multi-dose studies in healthy volunteers demonstrate stabilization of wild-type TTR
Tafamidis Inhibits TTR Amyloidogenesis via Kinetic Stabilization

Conclusions

- TTR tetramer destabilization leads to amyloid fibrils & other aggregates

- Tafamidis and interallelic trans-suppression similarly increase the dissociative activation barrier—the rate limiting step of amyloidogenesis—preventing amyloidogenesis

- Tafamidis stabilizes a range of TTR variants ex vivo and in patients
  - Suggestive of generalizability of tafamidis effect

- 20 mg daily dose is a rational and pharmacologically justified dosing regimen
Clinical Endpoints

Roy Freeman, MD
Professor of Neurology
Director, Center for Autonomic & Peripheral Nerve Disorders
Harvard Medical School, Boston, MA
The Challenge

How to quantify neuropathy and its progression with reliability and reproducibility with a disease modifying intervention

Background:

- No prior interventional trial in TTR-FAP
- No validated clinical assessment tool
- No validated endpoints for a trial
Neuropathy Impairment Score

- Most widely used quantitative assessment in diabetic polyneuropathy
- Lower Limb only (NIS-LL) (score 0-88)
- Components tested
  - Muscle Power [0 – 64]
  - Sensation [0 – 16]
  - Reflexes [0 – 8]
- Correlates with disease severity in DPN
  - NIS-LL increases by 0.9 pts/year in DPN
  - NIS-LL increase of 2 points clinically significant*

*Diabetic Neuropathy in controlled clinical trials: Consensus report of the peripheral nerve society. Annals of Neurology 1995; 478-481
NIS-LL: Muscle Groups

- Toe dorsiflexion
- Toe plantar flexion
- Ankle dorsiflexion
- Ankle plantar flexion
- Knee flexion
- Knee extension
- Hip flexion
- Hip extension

Scoring methodology:
- 0–4 points per side per muscle group
- Total of 64 points if paraplegic
NIS-LL: Reflex and Sensory Assessments

- Reflex
  - Quadriceps
  - Ankle

- Sensory
  - Pinprick
  - Touch pressure
  - Vibration (128 Hz tuning fork)
  - Joint position
Neurophysiology

- **Nerve Conduction Studies**
  - Sural nerve
  - Peroneal nerve
  - Tibial nerve

- **Quantitative Sensory Testing**
  - Vibratory threshold (great toe) - a large fiber function
  - Cooling sensory threshold and heat pain responses

- **Autonomic Assessment**
  - Heart rate response to deep breathing
## Summated (Σ) Scores of Neurophysiologic Function

<table>
<thead>
<tr>
<th>Σ7 – Primarily Large Fiber</th>
<th>Σ3 – Small fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vibration detection threshold</td>
<td>Cooling detection threshold</td>
</tr>
<tr>
<td>Heart rate variability with deep respiration</td>
<td>Heat pain</td>
</tr>
<tr>
<td>Nerve conduction studies</td>
<td>Heart rate variability with deep respiration</td>
</tr>
<tr>
<td>Peroneal nerve</td>
<td></td>
</tr>
<tr>
<td>Tibial nerve</td>
<td></td>
</tr>
<tr>
<td>Sural nerve</td>
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</table>
Primary Efficacy Endpoints in DPN Studies

- **NIS-LL as a continuous variable**

- **NIS-LL as a categorical variable**
  - e.g., response: <2 point change in NIS-LL

- **NIS-LL as a composite endpoint**
  - e.g., NIS-LL + Σ7
Norfolk QOL-Diabetic Neuropathy

- QOL instrument validated in DN*
- 5 Domains
  - Physical Functioning/Large Fiber Neuropathy
  - Activities of Daily Living
  - Symptoms
  - Small Fiber Neuropathy
  - Autonomic Neuropathy
- Total Quality of Life Score
  - Range of score: -2 to 138

Modified BMI (mBMI)

- Compensates for edema caused by low serum albumin
- Reflects neurogenic (autonomic bowel control), synthetic (liver production of albumin) and absorptive function (GI function)
- Correlates with disease severity, progression and mortality
- Well-validated prognostic factor for survival post liver transplant

$mBMI = BMI \times \text{serum albumin (g/L)}$

Suhr 1994; Suhr 2002; Suhr 2005
How Applicable Are Measures To TTR-FAP? Fx1A-OS-001 Study

- Observational, cross-sectional, single center study
- Objectives: evaluate endpoints in TTR-FAP program
- Population evaluated*
  - Healthy Volunteers N=16
  - TTR-FAP Stage I N=29
  - TTR-FAP Stage II N=16
  - TTR-FAP Stage III N=16
  Age and duration of disease appropriate for disease stage
- Assessments
  - NIS-LL, NIS-LL Subscales, Norfolk QOL-DN, mBMI, Σ7 and Σ3

* Stages According to: Coutinho in Amyloid and amyloidosis. Amsterdam. 1980; 88-98
NIS-LL Discriminates Across TTR-FAP Stages

NIS-LL (range 0-88)

<table>
<thead>
<tr>
<th></th>
<th>Mean Score</th>
<th>p-value</th>
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<tbody>
<tr>
<td>HV</td>
<td>n=16</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>n=29</td>
<td>p=0.002</td>
</tr>
<tr>
<td>Stage 2</td>
<td>n=16</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Stage 3</td>
<td>n=16</td>
<td>p&lt;0.0001</td>
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Study Fx1A-OS-001
HV = healthy volunteers
Pairwise p-values based on an analysis of variance without adjustment for multiple testing
**Neurophysiological Assessments**

**Σ7 NTs nds**

- **Stage 1** (n=29)
- **Stage 2** (n=16)
- **Stage 3** (n=16)

Mean

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Stage 1</td>
<td>20</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>Stage 2</td>
<td>25</td>
<td>NS</td>
</tr>
<tr>
<td>Stage 3</td>
<td>20</td>
<td>NS</td>
</tr>
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</table>

**Σ3 NTSF-LL nds**

- **Stage 1** (n=29)
- **Stage 2** (n=16)
- **Stage 3** (n=16)

Mean

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<th>Stage</th>
<th>Mean</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Stage 1</td>
<td>4</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>Stage 2</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Stage 3</td>
<td>10</td>
<td>NS</td>
</tr>
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Study Fx1A-OS-001

Pairwise p-values based on an analysis of variance without adjustment for multiple testing

NS = Not significant, p-value > 0.05
NIS-LL Subscales

Study Fx1A-OS-001
NS=Not significant, p-value > 0.05
Pairwise p-values based on an analysis of variance without adjustment for multiple testing
Muscle Weakness Progresses from Distal to Proximal

Study Fx1A-OS-001
HV = healthy volunteers, NS = Not significant, p-value > 0.05
Pairwise p-values based on an analysis of variance without adjustment for multiple testing

---

**Toe**

- HV: NS
- Stage 1: NS
- Stage 2: p<0.0001
- Stage 3: NS

**Ankle**

- HV: NS
- Stage 1: NS
- Stage 2: p<0.0001
- Stage 3: p=0.004

**Knee**

- HV: NS
- Stage 1: NS
- Stage 2: p≤0.0001
- Stage 3: p=0.0002

**Hip**

- HV: NS
- Stage 1: NS
- Stage 2: NS
- Stage 3: p<0.0001
Modified Body Mass Index Decreases with Disease Stage

**mBMI\(^1\)**

<table>
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<tr>
<th>Stage</th>
<th>Mean BMI</th>
<th>p-value</th>
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<tr>
<td>HV</td>
<td>1200</td>
<td>0.0447</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>1000</td>
<td>0.0017</td>
<td>NS</td>
</tr>
<tr>
<td>Stage 2</td>
<td>800</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Stage 3</td>
<td>600</td>
<td></td>
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NS=Not significant, p-value> 0.05
Pairwise comparisons without adjustment for multiple testing.

mBMI calculation: (kg/length in m\(^2\)) x serum albumin level (g/L)

1
Conclusion

- The differences and pattern of deficits detected by the NIS-LL, NIS-LL subscales and neurophysiology
  - Discriminate among disease stages
  - Biologically plausible
  - Consistent with the clinical course of the disease

- Thus, proposed endpoints
  - Sensitive indicators of disease severity
  - Appropriate to measure disease modifying treatment in TTR-FAP
Tafamidis Clinical Development Program

Donna Grogan, M.D.
Former Chief Medical Officer, FoldRx Inc.
Medical Consultant
Development Program Overview

- Efficacy Results
  - Study Fx-005
  - Study Fx-006
  - Study Fx1A-201

- Safety Results
**Tafamidis TTR-FAP Development Program**

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<th>Study Fx1A-303</th>
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<td>Open-label, multicenter, 36-month study</td>
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<td>Long-term safety and efficacy</td>
<td>Long-term extension study for Fx-006 and Fx1A-201 (study is ongoing)</td>
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Overview of Pivotal Study Fx-005

Screening

Randomization 1:1

Tafamidis 20 mg once daily

Placebo

18-Month Double-Blind Period
Main Entry Criteria
Fx-005

- Confirmed V30M mutation
  - Buccal swab
- Positive amyloid biopsy
- 18-75 years
- Karnofsky Performance Status score of ≥ 50
  - Able to care for most personal needs
- No history of liver transplantation
- Excluded patients with no vibratory sensation in both feet
Co-primary endpoints
- NIS-LL Responder (change from Baseline < 2) rate at Month 18*
- Norfolk QOL-DN TQOL Score change from Baseline to Month 18+

Key secondary endpoint
- NIS-LL Change from Baseline to Month 18^
Additional Secondary Endpoints
Fx-005

- Change from Baseline to each visit
  - NIS-LL total and subscales
  - TQOL score and domains
  - Σ3 (small nerve fiber function)
  - Σ7 (predominantly large nerve fiber function)
  - mBMI

- Proportion of patients with TTR stabilization
Pre-Specified Analysis Populations
Fx-005

### Intent-to-Treat (ITT) Population

Randomized patients
- who received at least 1 dose of study medication and
- had at least 1 post-baseline efficacy assessment for both the NIS-LL and TQOL or
- discontinued due to death or liver transplantation

### Efficacy Evaluable (EE) Population

ITT patients with non-missing NIS-LL and TQOL scores at Month 18
- took at least 80% of study medication
- had no important protocol deviations
Patient Disposition and Pre-Specified Populations
Fx-005

Screened
N=162

Safety population
n=128

ITT population
n=125

Completed 18 Months
n=91

Efficacy Evaluable Population
n=87

Reasons not included in ITT

<table>
<thead>
<tr>
<th>Tafamidis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative genotype</td>
<td>1</td>
</tr>
<tr>
<td>AE (no post-baseline evaluation)</td>
<td>1</td>
</tr>
</tbody>
</table>

Reasons not included in ITT

<table>
<thead>
<tr>
<th>Tafamidis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver transplantation</td>
<td>13</td>
</tr>
<tr>
<td>AE / Pregnancy</td>
<td>3</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>1</td>
</tr>
</tbody>
</table>

Reasons not included in EE population

<table>
<thead>
<tr>
<th>Tafamidis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important protocol deviation</td>
<td>2</td>
</tr>
</tbody>
</table>
### Distribution of Randomized Patients and TTR Transplant Recipients by Study Center Country

<table>
<thead>
<tr>
<th>Site</th>
<th>Number (%) Randomized</th>
<th>Percent of Liver Transplants reported to FAPWTR by Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portugal</td>
<td>78 (61) N=128</td>
<td>48%</td>
</tr>
<tr>
<td>Porto</td>
<td>74 (58)</td>
<td></td>
</tr>
<tr>
<td>Lisbon</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>74 (58)</td>
<td></td>
</tr>
<tr>
<td>Lisbon</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>9 (7)</td>
<td>12%</td>
</tr>
<tr>
<td>Sweden</td>
<td>10 (8)</td>
<td>7%</td>
</tr>
<tr>
<td>Argentina</td>
<td>10 (8)</td>
<td>1%</td>
</tr>
<tr>
<td>Brazil</td>
<td>13 (10)</td>
<td>5%</td>
</tr>
<tr>
<td>Spain</td>
<td>2 (2)</td>
<td>5%</td>
</tr>
<tr>
<td>Germany</td>
<td>6 (5)</td>
<td>3%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>0</td>
<td>4%</td>
</tr>
<tr>
<td>United States</td>
<td>0</td>
<td>4%</td>
</tr>
</tbody>
</table>

*From FAP Worldwide Transplant Registry (FAPWTR) ATTR-PN V30M liver transplant data; denominator n=1901*
Baseline Demographics
Fx-005 (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Tafamidis N=64</th>
<th>Placebo N=61</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>39.8 (12.7)</td>
<td>38.4 (12.9)</td>
<td>0.339</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>35.5 (25, 74)</td>
<td>34.0 (22, 71)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%), Female</td>
<td>32 (50.0)</td>
<td>35 (57.4)</td>
<td>0.410</td>
</tr>
<tr>
<td><strong>Disease Duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>47.0 (48.4)</td>
<td>34.7 (32.9)</td>
<td>0.319</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>28 (3, 268)</td>
<td>21 (2, 133)</td>
<td></td>
</tr>
</tbody>
</table>

* Continuous variable p-value based on Wilcoxon Rank Sum test; Categorical variables p-value based on a Chi-square test
## Baseline Disease Characteristics

**Fx-005 (ITT)**

<table>
<thead>
<tr>
<th></th>
<th>Tafamidis N=64</th>
<th>Placebo N=61</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NIS-LL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.4 (11.4)</td>
<td>11.4 (13.5)</td>
<td>0.089</td>
</tr>
<tr>
<td></td>
<td>4.0 (0, 54)</td>
<td>6.0 (0, 57)</td>
<td></td>
</tr>
<tr>
<td><strong>TQOL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>27.3 (24.2)</td>
<td>30.8 (26.7)</td>
<td>0.401</td>
</tr>
<tr>
<td></td>
<td>19 (-1, 110)</td>
<td>22 (0, 107)</td>
<td></td>
</tr>
<tr>
<td><strong>Small nerve (Σ3) fiber function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.5 (4.5)</td>
<td>5.6 (4.1)</td>
<td>0.998</td>
</tr>
<tr>
<td></td>
<td>4.8 (-4.5, 11.2)</td>
<td>5.0 (-3.7, 11.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Large nerve (Σ7) fiber function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7.8 (9.1)</td>
<td>8.7 (8.5)</td>
<td>0.582</td>
</tr>
<tr>
<td></td>
<td>7.4 (-13.6, 24.3)</td>
<td>9.7 (-10.6, 24.6)</td>
<td></td>
</tr>
<tr>
<td><strong>mBMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1005 (165.2)</td>
<td>1012 (212.9)</td>
<td>0.739</td>
</tr>
<tr>
<td></td>
<td>975 (655, 1510)</td>
<td>984 (533, 1582)</td>
<td></td>
</tr>
</tbody>
</table>

*p-values based on Wilcoxon Rank Sum test*
Co-Primary Endpoints
Fx-005

NIS-LL Responder Rate* (ITT)

<table>
<thead>
<tr>
<th>% of Responders (95% CI)</th>
<th>Tafamidis (N=64)</th>
<th>Placebo (N=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 Months</td>
<td>45.3</td>
<td>29.5</td>
</tr>
</tbody>
</table>

p = 0.068

* For the NIS-LL responder analysis, patients who discontinued study for a liver transplant (13 per group) were classified as non-responders Month 18; LOCF was used at Month 18 for all other discontinuations. p-value for NIS-LL responder analysis based on Chi-square test for proportions.
Co-Primary Endpoints
Fx-005

NIS-LL Responder Rate* (ITT)

% of Responders (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Tafamidis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=64</td>
<td>45.3</td>
<td>29.5</td>
</tr>
<tr>
<td></td>
<td>p = 0.068</td>
<td></td>
</tr>
</tbody>
</table>

18 Months

TQOL Change from Baseline (ITT, LOCF)

WORSENING

LS Mean (SE)

<table>
<thead>
<tr>
<th></th>
<th>Tafamidis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=64</td>
<td>2.0</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>p = 0.116</td>
<td></td>
</tr>
</tbody>
</table>

18 Months

* For the NIS-LL responder analysis, patients who discontinued study for a liver transplant (13 per group) were classified as non-responders Month 18; LOCF was used at Month 18 for all other discontinuations. p-value for NIS-LL responder analysis based on Chi-square test for proportions; p-value for TQOL based on ANCOVA with baseline as covariate.
Co-Primary Endpoints
Fx-005

NIS-LL Responder Rate*
(EE)

% of Responders (95% CI)

<table>
<thead>
<tr>
<th>Tafamidis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>60.0</td>
<td>38.1</td>
</tr>
</tbody>
</table>

N=45 N=42

18 Months

p = 0.041

* For the NIS-LL responder analysis, patients who discontinued study for a liver transplant (13 per group) were classified as non-responders Month 18; LOCF was used at Month 18 for all other discontinuations. p-value for NIS-LL responder analysis based on Chi-square test for proportions.
Co-Primary Endpoints
Fx-005

NIS-LL Responder Rate* (EE)

<table>
<thead>
<tr>
<th></th>
<th>Tafamidis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 18</td>
<td>60.0</td>
<td>38.1</td>
</tr>
</tbody>
</table>

p = 0.041

TQOL Change from Baseline (EE)

<table>
<thead>
<tr>
<th></th>
<th>Tafamidis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 18</td>
<td>0.1</td>
<td>8.9</td>
</tr>
</tbody>
</table>

p = 0.045

* For the NIS-LL responder analysis, patients who discontinued study for a liver transplant (13 per group) were classified as non-responders Month 18; LOCF was used at Month 18 for all other discontinuations. p-value for NIS-LL responder analysis based on Chi-square test for proportions; p-value for TQOL based on ANCOVA with baseline as covariate.
NIS-LL Responder Rate at Month 18 by Baseline Categories
Fx-005

Baseline NIS-LL Category (EE)

Responder (% of Patients)

<table>
<thead>
<tr>
<th>Category</th>
<th>Tafamidis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>41.2</td>
<td>58.3</td>
</tr>
<tr>
<td>4-8</td>
<td>82.4</td>
<td>41.7</td>
</tr>
<tr>
<td>&gt;8</td>
<td>54.5</td>
<td>22.2</td>
</tr>
</tbody>
</table>
NIS-LL Responder Rate at Month 18 by Baseline Categories
Fx-005

Below Q1
Median to Q3
Above Q3
Baseline NIS-LL Response Category (ITT)

Below Median
Above Median
Baseline NIS-LL Response Category (ITT)

Responder (% of Patients)

Baseline NIS-LL Category (EE)

Baseline NIS-LL Response Category (ITT)

Responder (% of Patients)

Tafamidis
Placebo

Responder (% of Patients)

Below Q1
Within IQR
Above Q3

Responder (% of Patients)
NIS-LL Responder Rate at Month 18 by Baseline Categories
Fx-005
NIS-LL Change from Baseline – Mixed Model Repeated Measures (MMRM) Fx-005 (ITT, OC)

p-values are based on a model with change from baseline as the dependent variable, treatment, month and treatment x month as fixed effects, subject as a random effect, and an unstructured covariance matrix.
NIS-LL Change from Baseline – Mixed Model Repeated Measures (MMRM) Fx-005 (ITT, OC)

**MMRM**

- **Tafamidis**
- **Placebo**

**MMRM with Baseline as Covariate**

*LS Mean (SE)*

- **Tafamidis n=64**
  - Months: 60, 49, 48
- **Placebo n=61**
  - Months: 57, 50, 47

*p-values are based on a model with change from baseline as the dependent variable, treatment, month and treatment x month as fixed effects, subject as a random effect, and an unstructured covariance matrix. Figure on right also includes baseline as a covariate.*
NIS-LL Change from Baseline – Mixed Model Repeated Measures (MMRM) Fx-005 (ITT, OC)

**MMRM**

- *Tafamidis* ▪ *Placebo*

---

**MMRM Sensitivity Analysis**

- Robustness to Outliers

---

- *Data from the 2 placebo patients with the highest values were replaced with data from a patient who had the third highest month 18 change value of 20.*

---

```
p-values are based on a model with change from baseline as the dependent variable, treatment, month and treatment x month as fixed effects, subject as a random effect, and an unstructured covariance matrix.
```
## NIS-LL Change from Baseline - Statistically Significant Across Analyses and Methodologies - Fx-005 (ITT)

<table>
<thead>
<tr>
<th>Analysis Method</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-specified Key Secondary: MMRM</td>
<td>0.027</td>
</tr>
<tr>
<td>MMRM with Baseline as Covariate*</td>
<td>0.043</td>
</tr>
<tr>
<td>MMRM Sensitivity Analysis**</td>
<td>0.039</td>
</tr>
<tr>
<td>Robustness to outliers</td>
<td></td>
</tr>
<tr>
<td>Multiple Imputation*</td>
<td>0.041</td>
</tr>
</tbody>
</table>

*Per European Authority requests.

**Data from the 2 placebo patients with the highest values were replaced with data from a patient who had the third highest month 18 change value of 20.
Favorable Effects of Tafamidis Primarily on NIS-LL Motor Exam Change from Baseline to Month 18 Subscale Analysis - Fx-005 (ITT,OC)

Key Secondary Endpoint

- **NIS-LL Month 18**: 5.8 (Tafamidis), 2.8 (Placebo), p=0.027
- **Motor**: 3.4 (Tafamidis), 0.8 (Placebo), p=0.013
- **Sensory**: 1.6 (Tafamidis), 1.3 (Placebo), p=0.637
- **Reflexes**: 0.8 (Tafamidis), 0.8 (Placebo), p=0.261

p-values are based on a model with change from baseline as the dependent variable, treatment, month and treatment x month as fixed effects, subject as a random effect, and an unstructured covariance matrix.
Favorable Effects of Tafamidis Primarily on NIS-LL Motor Exam Change from Baseline to Month 18 Subscale Analysis - Fx-005 (ITT,OC)

Key Secondary Endpoint

- **Motor**: p=0.013
- **Sensory**: p=0.637
- **Reflexes**: p=0.261

- **Toe**: p=0.009
- **Ankle**: p=0.016
- **Knee**: p=0.054
- **Hip**: p=0.835

p-values are based on a model with change from baseline as the dependent variable, treatment, month and treatment x month as fixed effects, subject as a random effect, and an unstructured covariance matrix.
Summary of NIS-LL Change from Baseline to Month 18 by Site Fx-005 (ITT, OC)

Drop out rate due to LT: 12.5% Portugal (Porto), 32% all other sites

Mean Change From Baseline to Month 18

- Portugal (Porto): Tafamidis 1.1, Placebo 5.4
- Portugal (Lisbon): Tafamidis 6.0, Placebo 19.0
- France: Tafamidis 1.0, Placebo 7.2
- Sweden: Tafamidis 4.3, Placebo 7.2
- Argentina: Tafamidis 3.6, Placebo 3.0
- Brazil: Tafamidis 6.7, Placebo 3.0
- Spain: Tafamidis 3.7, Placebo 5.7
- Germany: Tafamidis 3.7, Placebo 5.7
Σ7 Score – Change from Baseline to Month 18 by Site Fx-005

Mean Change From Baseline to Month 18

WORSENING

N= 30 31 1 1 3 0 4 3 4 3 4 0 0 3 3
Portugal (Porto) Portugal (Lisbon) France Sweden Argentina Brazil Spain Germany

Tafamidis
Placebo
Neurophysiologic Measures
Change from Baseline to Months 6, 12 and 18 – Fx-005 (ITT)

Σ7 (Predominantly Large Fiber)

Tafamidis  Placebo

WORSENING

50% preservation

p-values based on repeated measures analysis of variance
**Neurophysiologic Measures**

**Change from Baseline-Mixed Model Repeated Measures - Fx-005 (ITT, OC)**

### $\Sigma 7$ (Predominantly Large Fiber)

- **Tafamidis**
  - Months: 0, 6, 12, 18
  - LS Mean (SE): 0.0, 1.5, 2.5, 3.0
- **Placebo**
  - Months: 0, 6, 12, 18
  - LS Mean (SE): 0.0, 1.0, 2.0, 3.0

- **Worsening**
  - $p=0.012$ (Month 6), $p=0.066$ (Month 12), $p=0.050$ (Month 18)

### $\Sigma 3$ (Small Fiber)

- **Tafamidis**
  - Months: 0, 6, 12, 18
  - LS Mean (SE): 0.0, 0.5, 1.0, 1.5
- **Placebo**
  - Months: 0, 6, 12, 18
  - LS Mean (SE): 0.0, 0.5, 1.0, 1.5

- **Worsening**
  - $p=0.190$ (Month 6), $p=0.018$ (Month 12), $p=0.005$ (Month 18)

- **80% preservation**

---

$p$-values are based on a model with change from baseline as the dependent variable, treatment, month and treatment x month as fixed effects, subject as a random effect, and an unstructured covariance matrix.
mBMI - Change from Baseline- Mixed Model Repeated Measures Fx-005 (ITT, OC)

- p-values are based on a model with change from baseline as the dependent variable, treatment, month and treatment x month as fixed effects, subject as a random effect, and an unstructured covariance matrix.
TTR Stabilization
Fx-005 (ITT)

**Percentage of Patients Stabilized (95% CI)**

- **Week 8**: Tafamidis N=64, 98.4% (63% CI); Placebo N=61, 63% (60% CI)
- **Month 6**: Tafamidis N=64, 100% (95% CI); Placebo N=61, 59% (58% CI)
- **Month 12**: Tafamidis N=64, 97.9% (95% CI); Placebo N=61, 48% (50% CI)
- **Month 18**: Tafamidis N=64, 97.9% (95% CI); Placebo N=61, 48% (44% CI)
Consistent Results Across Efficacy Endpoints
Fx-005 (ITT)

- NIS-LL
- Muscle Weakness
- Reflexes
- Sensory
- TQOL
- Σ7
- Σ3
- mBMI/10

**mBMI/10** = modified body mass index divided by 10
The midpoint of each horizontal line represents the point estimate of the treatment effect for the change from baseline at Month 18

**Mean Change from Baseline at Month 18 (95% CI)**
Tafamidis Polyneuropathy Development Program

<table>
<thead>
<tr>
<th>Study Fx-005</th>
<th>Study Fx1A-201</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-month, randomized double-blind, placebo-controlled study</td>
<td>Pivotal study in V30M patients with TTR-FAP</td>
</tr>
<tr>
<td>Study Fx-005</td>
<td>Study Fx1A-201</td>
</tr>
<tr>
<td>12-month, open-label extension for Fx-005</td>
<td>Transthyretin stabilization in patients with non-V30M mutations</td>
</tr>
<tr>
<td>Study Fx-006</td>
<td>Study Fx1A-303</td>
</tr>
<tr>
<td>Long-term safety and efficacy</td>
<td>Open-label, multicenter, 36-month study</td>
</tr>
<tr>
<td>Study Fx1A-303</td>
<td>Long-term extension study for Fx-006 and Fx1A-201 (study is ongoing)</td>
</tr>
</tbody>
</table>
Objectives

- Safety
- Efficacy
  - Sustained treatment effect over 30 months with tafamidis continuation
  - Treatment effect with switch from placebo to tafamidis
  - Earlier-start treatment effect
- Blind from Study Fx-005 was maintained during the conduct of Study Fx-006
Patient Disposition
Fx-006

Fx-005
Double-blind placebo controlled

128 Patients Randomized

Fx-006
Open-label continuation (blind maintained)

Enrolled Fx-006 N=86

Tafamidis – Tafamidis n=45

Safety Population n=85

Tafamidis – Tafamidis n=44

Placebo – Tafamidis n=41

ITT Population
n=38

Completed n=33

ITT Population
n=33

Completed n=30
## Baseline Demographics
### Fx-006 (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Tafamidis-Tafamidis N=38</th>
<th>Placebo-Tafamidis N=33</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>Mean (SD)</td>
<td>42.0 (14.1)</td>
<td>40.7 (13.7)</td>
</tr>
<tr>
<td></td>
<td>Median (Range)</td>
<td>37.5 (26, 76)</td>
<td>36.0 (24, 73)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>n (%)</td>
<td>21 (55.3)</td>
<td>18 (54.5)</td>
</tr>
<tr>
<td><strong>Symptom duration, months</strong></td>
<td>Mean (SD)</td>
<td>61.6 (55.4)</td>
<td>53.7 (37.0)</td>
</tr>
<tr>
<td></td>
<td>Median (Range)</td>
<td>35.6 (21, 287)</td>
<td>36.8 (20, 152)</td>
</tr>
</tbody>
</table>

*p-values are based on Wilcoxon’s Rank Sum test for continuous variables and Fisher’s Exact Test for categorical variables*
## Baseline Disease Characteristics
### Fx-006 (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Tafamidis-Tafamidis N=38</th>
<th>Placebo-Tafamidis N=33</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIS-LL</td>
<td>Mean (SD) Median (Range)</td>
<td>8.4 (13.2) 5.3 (0, 65)</td>
<td>17.5 (20.8) 10.0 (0, 75)</td>
</tr>
<tr>
<td>TQOL</td>
<td>Mean (SD) Median (Range)</td>
<td>21.1 (21.9) 11.0 (-1, 97)</td>
<td>38.1 (31.9) 28.0 (-1, 96)</td>
</tr>
<tr>
<td>Σ7</td>
<td>Mean (SD) Median (Range)</td>
<td>6.7 (8.5) 5.0 (-6.6, 25.3)</td>
<td>10.1 (10.7) 10.8 (-7.3, 25.1)</td>
</tr>
<tr>
<td>Σ3</td>
<td>Mean (SD) Median (Range)</td>
<td>4.8 (4.3) 4.2 (-2.5, 11.2)</td>
<td>7.1 (4.4) 7.4 (-2.1, 11.2)</td>
</tr>
<tr>
<td>mBMI</td>
<td>Mean (SD) Median (Range)</td>
<td>1068.4 (142.4) 1038.1 (780.1, 1473.7)</td>
<td>990.1 (265.0) 945.7 (567.5, 1583.8)</td>
</tr>
</tbody>
</table>

* p-values based on Wilcoxon Rank Sum Test
NIS-LL Monthly Rate of Change
Fx-006 (ITT)

p-values comparing the rates of change based on a linear mixed model with the actual measurement as a dependent variable, study-by-treatment interaction and the time-by-study-by-treatment interaction as independent variables. The intercept and time variables were modeled as random effects.
p-values comparing the rates of change based on a linear mixed model with the actual measurement as a dependent variable, study-by-treatment interaction and the time-by-study-by-treatment interaction as independent variables. The intercept and time variables were modeled as random effects.
p-values comparing the rates of change based on a linear mixed model with the actual measurement as a dependent variable, study-by-treatment interaction and the time-by-study-by-treatment interaction as independent variables. The intercept and time variables were modeled as random effects.
TQOL Rate of Change
Fx-006 (ITT)

p-values comparing the rates of change based on a linear mixed model with the actual measurement as a dependent variable, study-by-treatment interaction and the time-by-study-by-treatment interaction as independent variables. The intercept and time variables were modeled as random effects.
p-values comparing the rates of change based on a linear mixed model with the actual measurement as a dependent variable, study-by-treatment interaction and the time-by-study-by-treatment interaction as independent variables. The intercept and time variables were modeled as random effects.
Neurophysiological Measures and mBMI
Fx-006 (ITT)

Σ7

WORSENING

Units/Month (SE)

Fx-005  Fx-006
Tafamidis-Tafamidis

Fx-005  Fx-006
Placebo-Tafamidis

p=0.930

p=0.213

Σ3

WORSENING

Units/Month (SE)

Fx-005  Fx-006
Tafamidis-Tafamidis

Fx-005  Fx-006
Placebo-Tafamidis

p=0.335

p=0.055

Σ

mBMI

WORSENING

Units/Month (SE)

Fx-005  Fx-006
Tafamidis-Tafamidis

Fx-005  Fx-006
Placebo-Tafamidis

p<0.0001

p=0.0006

p=0.213

p=0.055

Tafamidis-Tafamidis  Placebo-Tafamidis
NIS-LL Responder Status to Month 30
Fx-006 (ITT)

For Fx-005, Baseline is baseline of Fx-005
For Fx-006, Baseline is baseline of active treatment
TTR Stabilization
Fx-006

<table>
<thead>
<tr>
<th></th>
<th>Percentage of Patients Stabilized (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>Tafamidis: 94.6 ± 1.6</td>
<td>93.4–95.8</td>
</tr>
<tr>
<td></td>
<td>Placebo: 96.8 ± 0.8</td>
<td>95.9–97.7</td>
</tr>
<tr>
<td>Month 6</td>
<td>Tafamidis: 94.4 ± 1.4</td>
<td>92.7–96.1</td>
</tr>
<tr>
<td></td>
<td>Placebo: 96.9 ± 0.9</td>
<td>95.9–97.9</td>
</tr>
<tr>
<td>Month 12</td>
<td>Tafamidis: 94.1 ± 1.5</td>
<td>92.1–96.1</td>
</tr>
<tr>
<td></td>
<td>Placebo: 93.3 ± 1.7</td>
<td>91.6–95.0</td>
</tr>
</tbody>
</table>

- Tafamidis-Tafamidis
- Placebo-Tafamidis

Tafamidis N=37
Placebo N=31
Efficacy Summary
Fx-006

- Treatment benefits with tafamidis were maintained over 30 months
  - Consistency of response across double-blind and open-label treatment periods
  - >50% with no disease progression (NIS-LL responder)

- TTR stabilization was achieved in the placebo-tafamidis group; these patients experienced slower disease progression as measured by the clinical endpoints

- These data provide both internal replication of effect and serve as a source of confirmatory evidence of efficacy
## TTR-FAP Development Program

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
</table>
| Study Fx-005 | 18-month, randomized double-blind, placebo-controlled study  
  Pivotal study in V30M patients with TTR-FAP |
| Study Fx-006 | 12-month, open-label extension for Fx-005  
  Long-term safety and efficacy |
| Study Fx1A-201 | Open-label, multicenter, 12-month study  
  Transthyretin stabilization in patients with non-V30M mutations |
| Study Fx1A-303 | Open-label, multicenter, 36-month study  
  Long-term extension study for Fx-006 and Fx1A-201 (study is ongoing) |
Open label, 12-month study in patients with TTR-FAP who have a mutation other than V30M

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>TTR stabilization at 6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary Endpoints</strong></td>
<td>NIS (including NIS-LL), TQOL, Σ 5 (NCS), HRDB, mBMI</td>
</tr>
</tbody>
</table>

21 patients with 8 different mutations enrolled (N)

- Leu58His (4)*
- Ser77Tyr (2)*
- Ile107Val (2)
- Phe64Leu (4)*
- Gly47Ala (3)*
- Ser77Phe (1)
- Thr60Ala (4)*
- Asp38Ala (1)*

* TTR mutations reported from US in FAPWTR or enrolled from US site
## Baseline Demographics and Disease Characteristics

**Fx1A-201 (ITT)**

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Median (Range)</th>
<th>Fx-1A-201 Tafamidis N=21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Mean (SD)</td>
<td>Median (Range)</td>
<td>63.1 (9.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>64.3 (43.9, 76.8)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>n (%)</td>
<td></td>
<td>8 (38.1)</td>
</tr>
<tr>
<td><strong>mBMI</strong></td>
<td>Mean (SD)</td>
<td>Median (Range)</td>
<td>1052.5 (206.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1047.8 (725.0, 1409.6)</td>
</tr>
<tr>
<td><strong>Disease Duration (months)</strong></td>
<td>Mean (SD)</td>
<td>Median (Range)</td>
<td>64.7 (60.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45.5 (5.2, 253.1)</td>
</tr>
<tr>
<td><strong>NIS-LL</strong></td>
<td>Mean (SD)</td>
<td>Median (Range)</td>
<td>27.6 (24.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18.0 (0.0, 69.9)</td>
</tr>
<tr>
<td><strong>TQOL</strong></td>
<td>Mean (SD)</td>
<td>Median (Range)</td>
<td>47.8 (35.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>38.0 (5.0, 104.0)</td>
</tr>
<tr>
<td><strong>Σ5</strong></td>
<td>Mean (SD)</td>
<td>Median (Range)</td>
<td>6.1 (5.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.7 (-3.7, 14.8)</td>
</tr>
</tbody>
</table>
Primary Endpoint - TTR Stabilized Across Multiple Mutations Fx1A-201 (ITT)

Percentages at each visit calculated based on number of patients providing data for both baseline and that visit.

Week 6
N=19

Month 6
N=18

Month 12
N=17

Tafamidis 20 mg

Percentage of Patients Stabilized (95% CI)

94.7
100
100
# Secondary Endpoints - Change from Baseline to Month 12

<table>
<thead>
<tr>
<th></th>
<th>Fx1A-201 Mean (SD)</th>
<th>Fx-005 Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NIS-LL</strong></td>
<td>Tafamidis N=18</td>
<td>Tafamidis N=49</td>
</tr>
<tr>
<td><strong>Month 12</strong></td>
<td>2.70 (6.27)</td>
<td>1.35 (0.80)</td>
</tr>
<tr>
<td><strong>mBMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Month 12</strong></td>
<td>16.6 (89.33)</td>
<td>19.4 (10.23)</td>
</tr>
<tr>
<td><strong>Σ5 (NCS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Month 12</strong></td>
<td>0.20 (0.20)</td>
<td>0.70 (3.43)</td>
</tr>
<tr>
<td><strong>TQOL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Month 12</strong></td>
<td>-1.40 (11.71)</td>
<td>1.50 (2.31)</td>
</tr>
</tbody>
</table>
Summary
Fx1A-201

- TTR stabilization demonstrated across all mutations evaluated
- Effect maintained over 12 months of study
- Despite more severe disease, progression across measured endpoints is similar to that observed for the Fx-005 tafamidis treatment group
## Replication of Efficacy Across Endpoints

**Fx-005**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Benefit of Tafamidis Measured by Endpoint</th>
</tr>
</thead>
</table>
| **Co-Primaries**          | **NIS-LL**  
Norfolk TQOL  
Numerical differences favoring tafamidis (ITT)  
Statistically more NIS-LL responders and preserved QOL (EE)  
50% preservation of neurologic function (ITT), with persistence of effect when adjusting for baseline severity                                                                 |
| **Neurological Function** | (NIS-LL)  
Statistically significant 75% preservation of muscle strength  
Placebo with distal to proximal progression of muscle weakness                                                                                                          |
| **Neurophysiologic Function** | Statistically significant 80% preservation of small fiber function  
Trend for 50% preservation of large fiber function                                                                                                                    |
| **Modified BMI**          | Statistically significant improvement in mBMI                                                                                                                               |
| **TTR Stabilization**     | >97% of patients demonstrate stabilization of TTR tetramer                                                                                                                 |
Additional Confirmatory Evidence of Efficacy
Fx-006, Fx1A-201

- Persistence of effect
  - >50% of patients with no disease progression (NIS-LL responder analysis) through 30 months of treatment

- Replication of results
  - Statistically significant or numerical slowing of disease across all endpoints in placebo patients upon initiation of tafamidis treatment

- Generalizability
  - Similar effects observed in patients with mutations other than V30M
  - TTR stabilization demonstrated across all genotypes in clinical studies

Totality of the data support the original hypothesis that stabilization of the TTR tetramer by tafamidis does translate to slowing disease progression in patients with TTR-FAP
Tafamidis Safety
Tafamidis Exposure in TTR-FAP as of 31 Dec 2011 (Studies Fx-005, Fx-006, Fx1A-201, Fx1A-303)

127 TTR-FAP patients treated with Tafamidis
## Discontinuations Due to Adverse Events (Fx-005)

### Discontinuations

<table>
<thead>
<tr>
<th>Primary Reason, n (%)</th>
<th>Tafamidis N=65</th>
<th>Placebo N=63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>4 (6.2)</td>
<td>3 (4.8)</td>
</tr>
<tr>
<td>Patient Withdrew Consent</td>
<td>1 (1.5)</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>Liver Transplant</td>
<td>13 (20.0)</td>
<td>13 (20.6)</td>
</tr>
<tr>
<td>Patient Died</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
</tbody>
</table>

### Discontinuations Due to AEs

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Onset Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Day 133</td>
</tr>
<tr>
<td>Nausea</td>
<td>Day 16</td>
</tr>
<tr>
<td>Urticaria*</td>
<td>Day 190</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Day 169</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tafamidis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue, Paresthesia</td>
<td>Day 167</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, Unintentional weight loss</td>
<td>Day 38</td>
</tr>
<tr>
<td>Worsening Cardiac amyloidosis*</td>
<td>Day 409</td>
</tr>
</tbody>
</table>

* Serious adverse event
## Most Common AEs (≥10%)  
**Fx-005**

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>Tafamidis N=65</th>
<th>Placebo N=63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with at least 1 AE</td>
<td>60 (92.3)</td>
<td>61 (96.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 (26.2)</td>
<td>11 (17.5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>15 (23.1)</td>
<td>8 (12.7)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>11 (16.9)</td>
<td>6 (9.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (15.4)</td>
<td>12 (19.0)</td>
</tr>
<tr>
<td>Influenza</td>
<td>10 (15.4)</td>
<td>9 (14.3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9 (13.8)</td>
<td>8 (12.7)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>8 (12.3)</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (12.3)</td>
<td>8 (12.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (10.8)</td>
<td>8 (12.7)</td>
</tr>
<tr>
<td>Lacrimation decreased</td>
<td>6 (9.2)</td>
<td>7 (11.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (6.2)</td>
<td>7 (11.1)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>4 (6.2)</td>
<td>8 (12.7)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>2 (3.1)</td>
<td>7 (11.1)</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>3 (4.6)</td>
<td>10 (15.9)</td>
</tr>
<tr>
<td>Neuralgia</td>
<td>2 (3.1)</td>
<td>12 (19.0)</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>2 (3.1)</td>
<td>7 (11.1)</td>
</tr>
</tbody>
</table>

= Tafamidis > Placebo
## Serious Adverse Events (SAEs)  
*Fx-005*

<table>
<thead>
<tr>
<th>Tafamidis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6 patients (9.2%) with SAEs</strong></td>
<td><strong>5 patients (7.9%) with SAEs</strong></td>
</tr>
<tr>
<td>Viral Infection</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td></td>
<td>Cardiac Amyloidosis</td>
</tr>
<tr>
<td>Conduction disorder</td>
<td>Syncope, Anemia</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Staphylococcal infection – pacemaker site;</td>
</tr>
<tr>
<td></td>
<td>Lymphangitis, Cellulitis – right leg; Cellulitis – left foot; Skin Ulcer – left foot</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>Hypertensive emergency; Third degree burns</td>
</tr>
<tr>
<td>Localized Infection – foot</td>
<td>Nausea; Vomiting; Catheter site phlebitis</td>
</tr>
<tr>
<td>Pneumonia, UTI</td>
<td></td>
</tr>
</tbody>
</table>
## Deaths in Fx-005 (all occurred post-liver transplant)

<table>
<thead>
<tr>
<th>Tafamidis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac tamponade (following pacer placement for liver transplantation)</td>
<td>Sepsis (approximately 6 months after liver transplantation)</td>
</tr>
<tr>
<td>Unknown cause (approx. 3 months after liver transplantation at a different hospital)</td>
<td>Hepatic Failure (following transplant, died despite re-transplantation)</td>
</tr>
<tr>
<td>Unknown cause (10 days after liver transplant)</td>
<td></td>
</tr>
<tr>
<td>Description</td>
<td>Tafamidis N=65 (%)</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Number of patients with ≥1 UTI</td>
<td>17 (26.2)</td>
</tr>
<tr>
<td>Gender (Female : Male)</td>
<td>12:5</td>
</tr>
<tr>
<td>Number patients with Serious UTIs</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Number of patients treated with antibiotics</td>
<td>16 (94.1)</td>
</tr>
<tr>
<td>Number of patients with mild or moderately severe UTI</td>
<td>16 (94.1)</td>
</tr>
<tr>
<td>Number of patients who discontinued study drug</td>
<td>0</td>
</tr>
<tr>
<td>Number of patients recovered/recovering</td>
<td>16 (94.1)</td>
</tr>
</tbody>
</table>
Additional Safety Topics
Fx-005

- **Thyroid function**
  - Labs: extensive monitoring of TSH, T4, FT4
  - AE Data: 2 tafamidis-treated patients and 1 placebo-treated patient with thyroid-related AEs
  - No evidence of adverse treatment effect

- **Liver function**
  - Labs: extensive monitoring of ALT, AST, TB, GGT, AP
  - AE Data: 2 tafamidis-treated patients and 1 placebo-treated patient with transaminase elevations (TB within reference range) and 1 placebo-treated patient
  - Low potential for drug-induced liver injury

- **Blood pressure & Heart rate**
  - No evidence of adverse treatment effect

- **ECGs (QTc)**
  - No evidence of adverse treatment effect, low potential for cardiac repolarization abnormalities
### Adverse Drug Reactions in Labeling

#### Controlled Study Fx-005

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Tafamidis N=65</th>
<th>Placebo N=63</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 (26.2)</td>
<td>12 (19.0)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>8 (12.3)</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection†</td>
<td>17 (26.2)</td>
<td>9 (14.3)</td>
</tr>
<tr>
<td>Vaginal infection*</td>
<td>6 (9.2)</td>
<td>3 (4.8)</td>
</tr>
</tbody>
</table>

† Preferred term: UTI, Escherichia UTI and Cystitis
* Preferred term: Vaginal infection, Vaginal candidiasis, Candidiasis
## Tafamidis Pharmacovigilance & Risk Management Activities

<table>
<thead>
<tr>
<th>Current &amp; planned Pharmacovigilance &amp; Risk Management Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Labeling safety communication</strong></td>
</tr>
<tr>
<td><strong>Collection of AE reports and use of Data Capture Aids</strong></td>
</tr>
<tr>
<td>• Thyroid dysfunction</td>
</tr>
<tr>
<td>• Hypersensitivity reactions</td>
</tr>
<tr>
<td>• Hepatotoxicity</td>
</tr>
<tr>
<td><strong>Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO)</strong></td>
</tr>
<tr>
<td>• 12 month post-birth follow-up questionnaire (in addition to routine exposure in utero follow-up)</td>
</tr>
<tr>
<td><strong>Transthyretin Amyloidosis Outcomes Survey (THAOS)</strong></td>
</tr>
<tr>
<td>• Disease registry to collect data on carriers of all mutations, regardless of treatment</td>
</tr>
<tr>
<td><strong>Study Fx1A-303</strong></td>
</tr>
<tr>
<td>• Ongoing collection of safety &amp; efficacy data</td>
</tr>
</tbody>
</table>
Summary of Tafamidis Safety Profile

- Generally well tolerated in clinical trials
  - Low discontinuation rate due to AEs
  - Adverse Drug Reactions are manageable
  - Many AEs observed are consistent with TTR-FAP disease morbidity
  - No identified safety trends in laboratory, vital sign or ECG data

- Identified & potential risks are acceptable in the context of the morbidity and mortality of the disease and liver transplant

- Ongoing collection of safety data through routine pharmacovigilance, clinical trials, TESPO and THAOS
TTR-FAP Clinical Perspective

Teresa Coelho, MD
Santo Antonio Hospital, Porto, Portugal
TTR-FAP Geographical Distribution
Porto, The Largest Center to Study TTR-FAP

- TTR-FAP identified in the 1930s by Dr. Andrade in Porto, Portugal
- Portugal is the most important endemic region in the world:
  - Prevalence is higher than 1/1000 in some districts
- Santo António Hospital is the largest treatment facility for TTR-FAP in the world
  - 700 patients and 300 genetic carriers followed each year
  - 80-100 new patients diagnosed each year
- 48% of FAPWTR patients are from Portugal
Porto Experience with Tafamidis

- We enrolled 74 patients
- 44 are currently on treatment
  - 22 for nearly 5 years
  - 22 for 3 ½ years
- All patients remain in Stage 1
TTR-FAP Across Variants and Geographical Regions

- FAP is a heterogeneous condition, both genetically and clinically
- Even in Portugal we see heterogenicity
  - Non-V30M mutations present
  - Age of onset varies (20-80 years)
  - Additional organ involvement
- Disease characteristics and pattern of progression for polyneuropathy are similar:
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  - Always a length dependent sensory motor and autonomic neuropathy
  - Severe progression invariably leading to a fatal outcome
  - For patients who present with neuropathy the life expectancy from onset of first symptoms is similar across variants and regions

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Tafamidis Benefit:Risk

Ilise Lombardo, M.D.
Medicines Development Group Lead, Tafamidis
Pfizer Inc
Potential Pathways for Approval for Tafamidis

- **Traditional approval**
  - Substantial evidence of clinical benefit
  - Confirmatory evidence established

- **Accelerated (Subpart H) Approval**
  - Substantial evidence of effect on clinical endpoints or biomarker endpoint that is reasonably likely to predict clinical benefit
  - Post-approval confirmatory study required
## Endpoints for Replication of Efficacy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Benefits Measured by Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Co-Primaries</td>
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<td>Neuropathy Impairment Score-LL (NIS-LL) &amp; Norfolk Quality of Life Questionnaire</td>
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<td>• <strong>Neurophysiologic Function</strong> $\Sigma 3, \Sigma 7$</td>
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</tr>
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<td>• <strong>Modified BMI</strong></td>
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</tr>
<tr>
<td>• TTR Stabilization</td>
<td>Blocks rate-limiting step in disease – biologically plausible marker</td>
</tr>
</tbody>
</table>


Primary Endpoints: Evidence of Clinical Benefit

**Intent to Treat**

- **Tafamidis:**
  - NIS-LL Responder: 45.3% (95% CI)
  - N = 64

- **Placebo:**
  - NIS-LL Responder: 29.5% (95% CI)
  - N = 61

**Efficacy Evaluable**

- **Tafamidis:**
  - NIS-LL Responder: 60.0% (95% CI)
  - N = 45

- **Placebo:**
  - NIS-LL Responder: 38.1% (95% CI)
  - N = 42

**TQOL Change from Baseline**

- **Tafamidis:**
  - LS Mean (SE): 2.0 (2.0)
  - N = 64

- **Placebo:**
  - LS Mean (SE): 7.2 (7.2)
  - N = 61

**Worsening**

- **Tafamidis:**
  - LS Mean (SE): 0.1 (0.1)
  - N = 45

- **Placebo:**
  - LS Mean (SE): 8.9 (8.9)
  - N = 42

**P-values:**

- **Intent to Treat:** p = 0.068
- **Efficacy Evaluable:** p = 0.041
- **TQOL Change from Baseline:** p = 0.045
- **Worsening:** p = 0.116
Consistent Effects Across Independent Efficacy Measures of Disease Progression at 18 Months – Fx-005

**Neurophysiology**

<table>
<thead>
<tr>
<th>mBMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>-33.8</td>
</tr>
</tbody>
</table>

**NIS-LL Muscle Strength**

<table>
<thead>
<tr>
<th>Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toe</th>
<th>Ankle</th>
<th>Knee</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7</td>
<td>1.3</td>
<td>0.3</td>
<td>1.3</td>
</tr>
<tr>
<td>0.1</td>
<td>1.3</td>
<td>0.6</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**mBMI**

<table>
<thead>
<tr>
<th>p&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>39.3</td>
</tr>
</tbody>
</table>

<table>
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<th>mBMI</th>
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<td>-33.8</td>
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**Tafamidis N=64**

**Placebo N=61**
Consistent Effects Across Independent Efficacy Measures of Disease Progression at 18 Months – Fx-005

**Neurophysiology**

- **Σ3**
  - Tafamidis N=64: 0.34
  - Placebo N=61: 1.62
  - p=0.005
- **Σ7**
  - Tafamidis N=64: 1.52
  - Placebo N=61: 3.17
  - p=0.066

**NIS-LL Muscle Strength**

- **Motor**
  - Tafamidis N=64: 0.8
  - Placebo N=61: 3.4
  - p=0.013
- **Toe, Ankle, Knee, Hip**
  - Tafamidis N=64: 0.3, 1.3, 0.3, 0.2
  - Placebo N=61: 1.3, 1.3, 0.6
  - p=0.009, 0.016, 0.054

**mBMI**

- Tafamidis N=64: 39.3
- Placebo N=61: -33.8
- p<0.0001
FX-006 Provides Confirmatory Support to FX-005

Neurophysiology

<table>
<thead>
<tr>
<th></th>
<th>Units/Months (SE)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fx-005</td>
<td>0.18</td>
<td>Fx-006</td>
</tr>
</tbody>
</table>

\[ \sum 7 \]

p=0.213

WORSENING

<table>
<thead>
<tr>
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<th>Units/Months (SE)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Fx-005</td>
<td>0.09</td>
<td>Fx-006</td>
</tr>
</tbody>
</table>

\[ \sum 3 \]

p=0.055

NIS-LL

Fx-005 N=33   Fx-006 N=31

12 months (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Placebo-Tafamidis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units/Months (SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fx-005</td>
<td>0.34</td>
<td>0.16</td>
</tr>
</tbody>
</table>

\[ \text{NIS-LL} \]

p=0.010

TQOL/ mBMI

\[ \text{TQOL} \]

p=0.0003

\[ \text{mBMI} \]

p<0.0001

<table>
<thead>
<tr>
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<th>Units/Months (SE)</th>
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</thead>
<tbody>
<tr>
<td>Fx-005</td>
<td>0.61</td>
<td>Fx-006</td>
</tr>
<tr>
<td>Fx-005</td>
<td>-1.77</td>
<td>Fx-006</td>
</tr>
</tbody>
</table>

\[ \text{WORSENING} \]
TTR Stabilization Across the Tafamidis Program

**Fx-005**
- **Tafamidis-Placebo**
  - Week 8: 98%
  - Month 6: 100%
  - Month 12: 98%
  - Month 18: 98%

**Tafamidis-Tafamidis**
- Week 6: 95%
- Month 6: 97%
- Month 12: 94%
- Month 18: 93%

**Placebo-Placebo**
- Week 6: 95%
- Month 6: 100%
- Month 12: 100%

**Fx-006**
- **Tafamidis-Placebo**
  - Week 6: 95%
  - Month 6: 94%
  - Month 12: 94%

**Tafamidis-Tafamidis**
- Week 6: 97%
- Month 6: 97%
- Month 12: 93%

**Placebo-Placebo**
- Week 6: 97%
- Month 6: 93%
- Month 12: 93%

**Fx-1A-201**
- **Tafamidis-Placebo**
  - Week 6: 95%
  - Month 6: 100%
  - Month 12: 100%

**Tafamidis-Tafamidis**
- Week 6: 95%
- Month 6: 100%
- Month 12: 100%

**Placebo-Placebo**
- Week 6: 95%
- Month 6: 100%
- Month 12: 100%
Tafamidis is Safe and Well Tolerated

- No significant safety concerns
- Overall AE and SAE rates similar to placebo
  - Imbalances in GI and GU events
  - Manageable and reversible
- Does not alter standard practice for liver transplant evaluation
Pfizer established the THAOS* Registry in 2007
- Well-established, international disease registry
- Patients with TTR amyloidosis and asymptomatic carriers
- Vehicle to monitor patients and collect prospective data in the real world setting
  - Untreated patients
  - Patients on tafamidis
  - Patients post-liver transplant
- Data as of February 2012
  - 46 sites across 19 countries
  - 1226 total participants

*Transthyretin Amyloidosis Outcomes Survey
Options for a Post-approval Confirmatory trial

- THAOS registry
  - Non-randomized tafamidis versus untreated patients
- Prospective open-label treatment versus historic control
- Double-blind placebo controlled study using NIS-LL Muscle Weakness subscale plus a patient reported or functional outcome measure
- TTR-Cardiomyopathy
Results demonstrate replication and consistent results across endpoints and studies
- Primary endpoints support clinical benefit
- Secondary endpoints encompass a range of measures of disease progression reasonably likely to predict clinical benefit

TTR stabilization translates into clinical benefit across studies

Positive Benefit:Risk profile supported by totality of data justifies approval
Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP) is a life-threatening disorder with no pharmacologic treatment available.

- Ultra-rare disease
- Neuropathy affects small and large nerve fibers resulting in sensory, motor and autonomic dysfunction
  - Progressive disability at prime of life (age 30 – 50 years)
  - Fatal within 10-15 years of diagnosis (mean survival)

- Only available intervention is liver transplantation
  - High risk procedure
  - Not suitable or available for every patient
  - Lifelong immunosuppressive therapy

Pharmacologic treatment desperately needed.
NIS-LL Change from Baseline by Week 8 TTR Stabilization Status at Months 6, 12, and 18 (ITT)

Week 8 Stabilized N=66
(Tafamidis n=62, Placebo n=4)

Week 8 Not Stabilized N=57
(Tafamidis n=1, Placebo n=56)

p-values are based on a model with change from baseline as the dependent variable, TTE stabilization at week 8, month and TTR stabilization at week 8 by month interaction as fixed effects, subject as a random effect, and an unstructured covariance matrix.

E130
Norfolk QOL-DN Domain Scores, Least Square Mean Change from Baseline to 18 Months from an MMRM Analysis (ITT, OC)

p-values based on repeated measures analysis of variance with change from baseline as the dependent variable, treatment, month and treatment-by-month as fixed effects and subject as a random effect in the model, and an unstructured covariance matrix.
## Fx-005 - Baseline Disease Characteristics For Subjects who had Liver Transplant (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Liver Transplant</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tafamidis</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=13</td>
<td>N=13</td>
<td></td>
</tr>
<tr>
<td>NIS-LL</td>
<td>Mean (SD)</td>
<td>15.1 (15.64)</td>
<td>13.8 (14.04)</td>
</tr>
<tr>
<td></td>
<td>Median (Range)</td>
<td>10.0 (2.0, 53.5)</td>
<td>10.5 (2.0, 51.9)</td>
</tr>
<tr>
<td>TQOL</td>
<td>Mean (SD)</td>
<td>43.7 (20.38)</td>
<td>37.8 (21.18)</td>
</tr>
<tr>
<td></td>
<td>Median (Range)</td>
<td>46.0 (12.0, 71.0)</td>
<td>33.0 (15.0, 86.0)</td>
</tr>
<tr>
<td>Σ 7</td>
<td>Mean (SD)</td>
<td>12.7 (8.38)</td>
<td>13.0 (5.66)</td>
</tr>
<tr>
<td></td>
<td>Median (Range)</td>
<td>14.0 (-2.4, 24.3)</td>
<td>11.4 (4.9, 23.2)</td>
</tr>
<tr>
<td>Σ 3</td>
<td>Mean (SD)</td>
<td>8.1 (4.31)</td>
<td>7.1 (3.34)</td>
</tr>
<tr>
<td></td>
<td>Median (Range)</td>
<td>11.2 (0.6, 11.2)</td>
<td>7.9 (2.4, 11.2)</td>
</tr>
<tr>
<td>mBMI</td>
<td>Mean (SD)</td>
<td>993.1 (181.49)</td>
<td>957.9 (165.62)</td>
</tr>
<tr>
<td></td>
<td>Median (Range)</td>
<td>1028.7 (655.1, 1249.6)</td>
<td>958.2 (757.9, 1275.1)</td>
</tr>
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</table>
Fx-005
Change from Baseline in Efficacy Endpoints at Month 6 in Subjects who Discontinued due to Liver Transplant

<table>
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<th>Endpoint</th>
<th>Tafamidis Mean (SD)</th>
<th>Placebo Mean (SD)</th>
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<tr>
<td>NIS-LL</td>
<td>2.7, 5.1</td>
<td>4.8</td>
</tr>
<tr>
<td>TQOL</td>
<td>-1.7, 1.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Sum 7</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Sum 3</td>
<td>2.6</td>
<td>3.94</td>
</tr>
<tr>
<td>mBMI/10</td>
<td>-2.13</td>
<td></td>
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Tafamidis n= 9  Placebo n= 9
MMRM NIS-LL Change from Baseline: Site-by-Treatment Interaction (Across Visits)

P-values are based on a MMRM model with change from baseline as the dependent variable, treatment, site, treatment by site interaction, and treatment by month by site interaction as independent variables. An unstructured covariance matrix was used.
Fx-005 HRDB Normal Deviates
Change from Baseline to Months 6, 12 and 18 (ITT, OC)

Baseline: Tafamidis = -1.6
Placebo = -1.4

p=0.35  p=0.10  p=0.14

p-values based on repeated measures analysis of variance with change from baseline as the dependent variable, treatment, month and treatment x month as fixed effects, subject as a random effect, and an unstructured covariance matrix.
Study Fx-005
Sample Size Assumptions

- 50% response rate on active version 20% on placebo (at least 90% power and alpha 0.05)
- N=58 per group
- Sample size included an expectation of a 5%-10% dropout rate
- Total planned N=60 per group
- Actual enrollment=128
- For the co-primary endpoint TQOL, N=58 per group gives at least 90% power to detect a true difference between the tafamidis and Placebo groups that is 0.6 SD with a significance level of $\alpha = 0.05$ (two-sided)
Fx-005 Tafamidis Point Estimates and 95% Confidence Intervals (Placebo-Adjusted) for Key Efficacy Endpoints at Month 18 by Site (ITT)

Note: The midpoint of each horizontal line represents the point estimate of the treatment effect for the mean changes at Month 18 for each endpoint; the limits represent the 95% confidence intervals about the point estimates.
Tafamidis Stabilizes TTR Under Physiological Conditions

Tafamidis; $K_{d1} = 2 \text{ nM}; K_{d2} = 154 \text{ nM}$