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

Indication

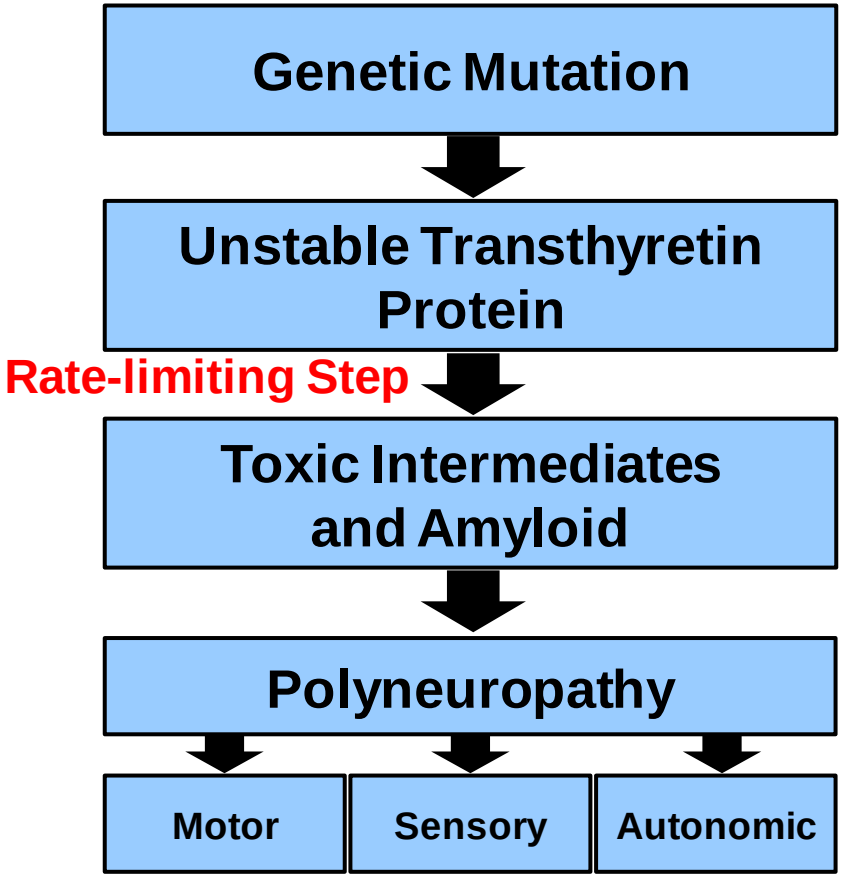
- Tafamidis - proposed trade name Vyndaqel®

- 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 **trans**port protein for **thy**roxine and **retin**ol binding complex
- Transthyretin Familial Amyloid Polyneuropathy, or TTR-FA**P**, is one of two major phenotypes of familial amyloidoses. The other is Transthyretin Familial Amyloid Cardiomyopathy, or TTR-FA**C**, which is the subject of a separate development program.

TTR Instability and Amyloid Cascade are Key Features of TTR-FAP

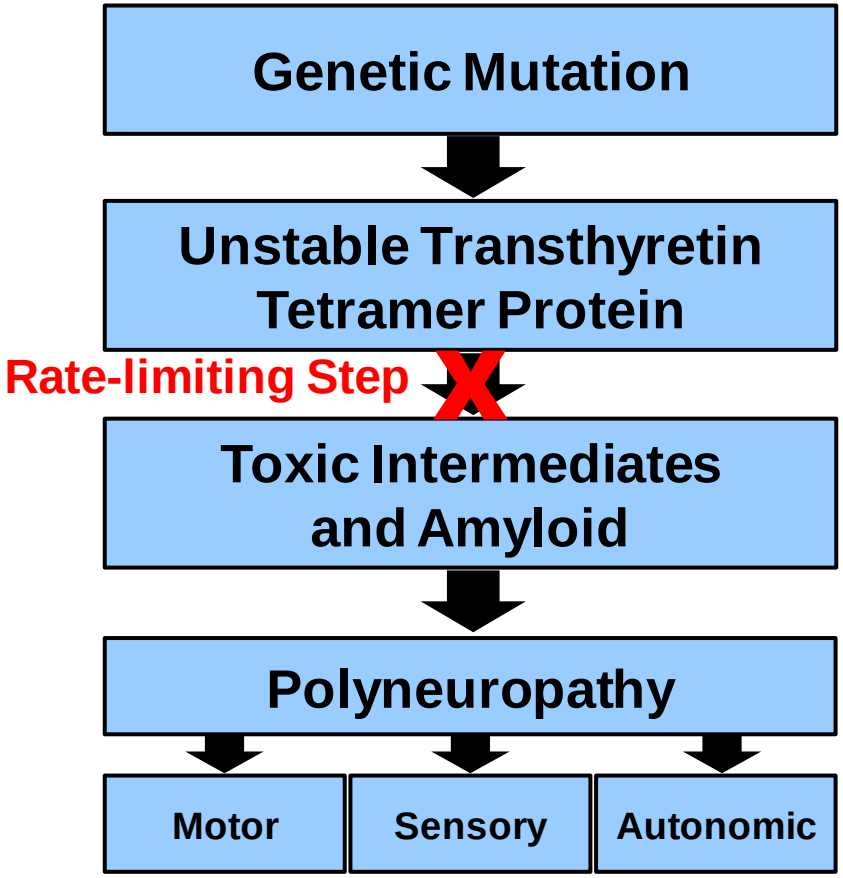


- TTR-FAP: rare and fatal autosomal dominant genetic disease

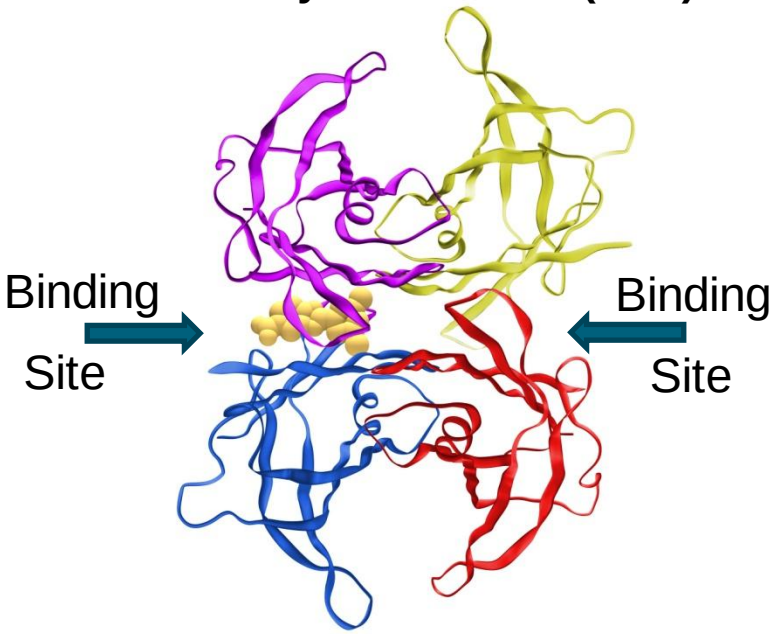
  Prevalence <10,000 patients worldwide

- 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

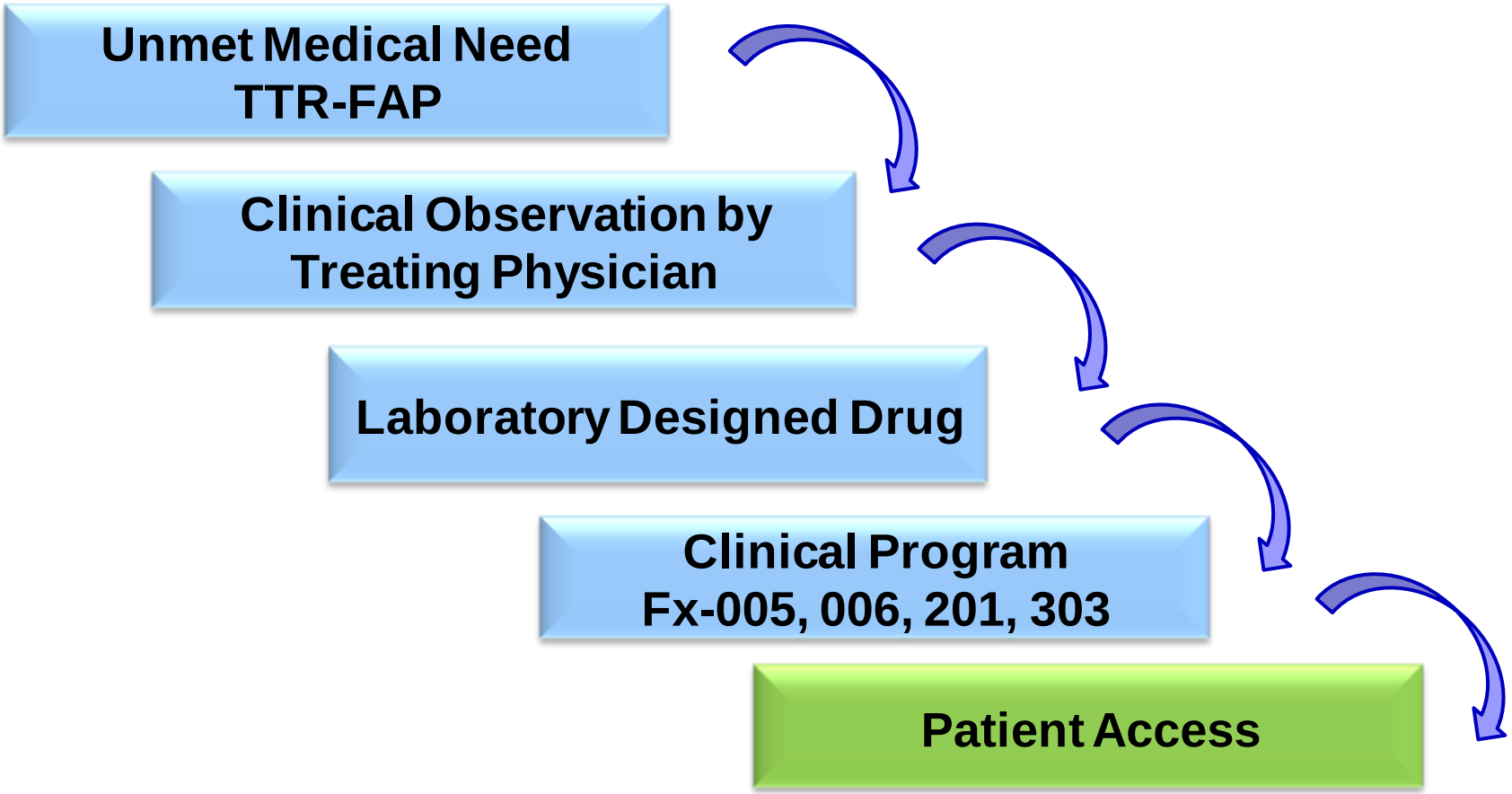


Tafamidis-Stabilized Transthyretin Protein (TTR)



Tafamidis designed to bind at thyroxine binding site to stabilize tetramer and block amyloid cascade

Tafamidis: Bench to Bedside Drug Development



Regulatory and Marketing Status

- 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

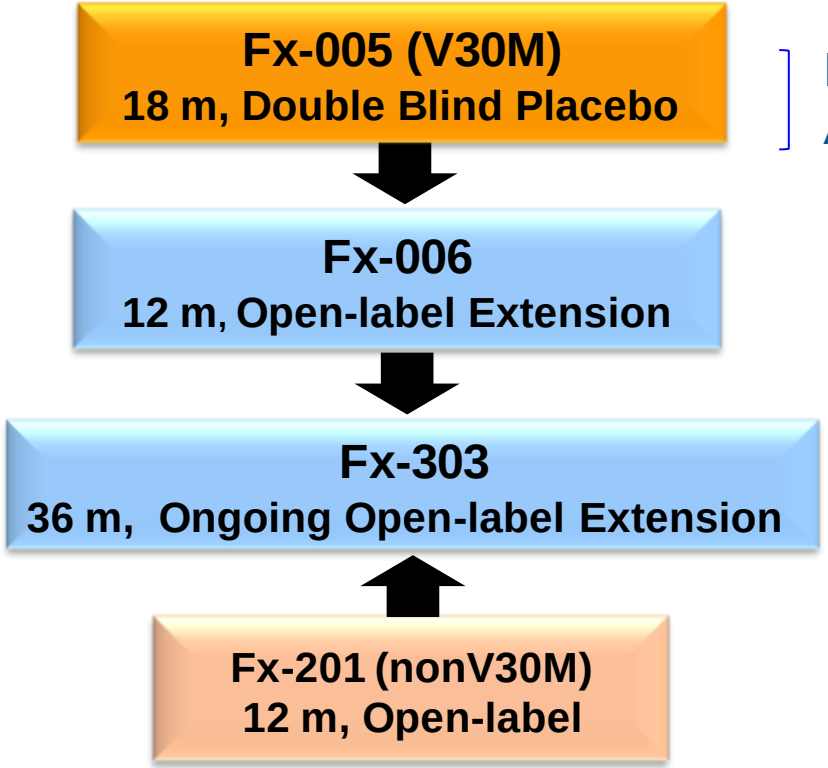
Considerations for Development of Tafamidis

- 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

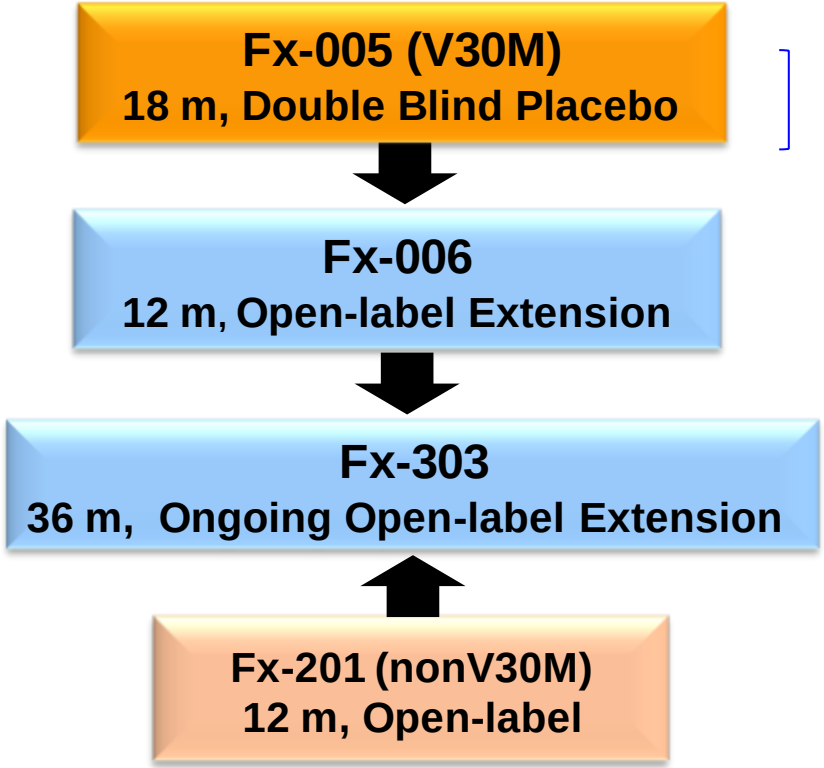
Endpoint	Benefits Measured by Endpoint
• **Co-Primaries** Neuropathy Impairment Score-LL (NIS-LL) & Norfolk Quality of Life Questionnaire	Clinical benefit
• **Neurologic Function** NIS-LL and subscales (motor, sensory, reflex)	Measures of disease progression – likely to predict clinical benefit
• **Neurophysiologic Function**	Measures of disease progression – likely to predict clinical benefit
• **Modified BMI**	Measure of overall disease severity with prognostic value in TTR-FAP – likely to predict clinical benefit in this setting of TTR-FAP
• **TTR Stabilization**	Blocks rate-limiting step in disease – biologically plausible marker

Core Clinical Program



Replication of Efficacy
Across Endpoints

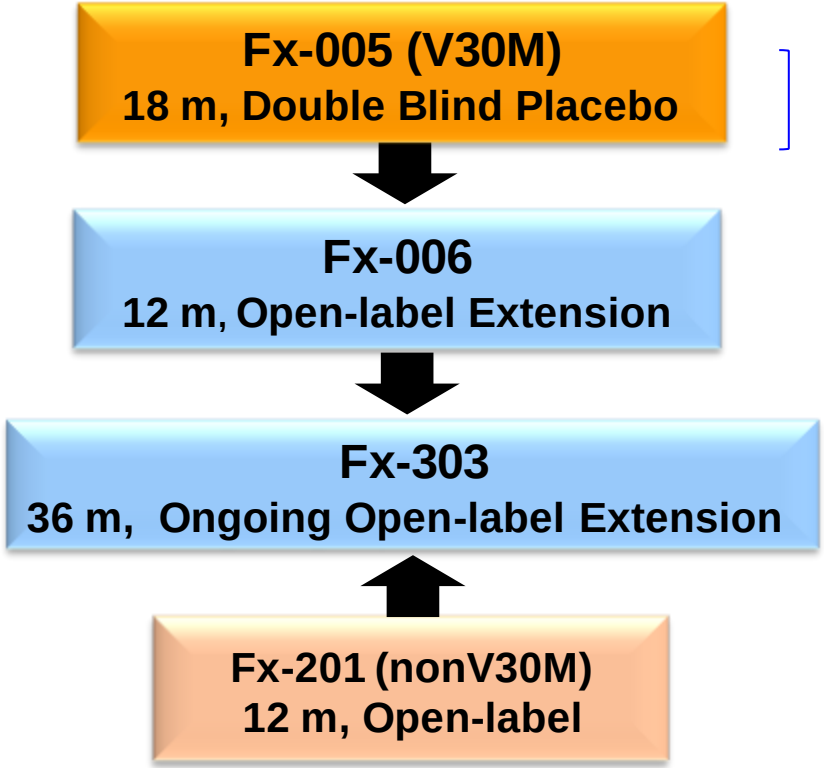
Core Clinical Program



Replication of Efficacy Across Endpoints

Confirmatory Evidence

Core Clinical Program

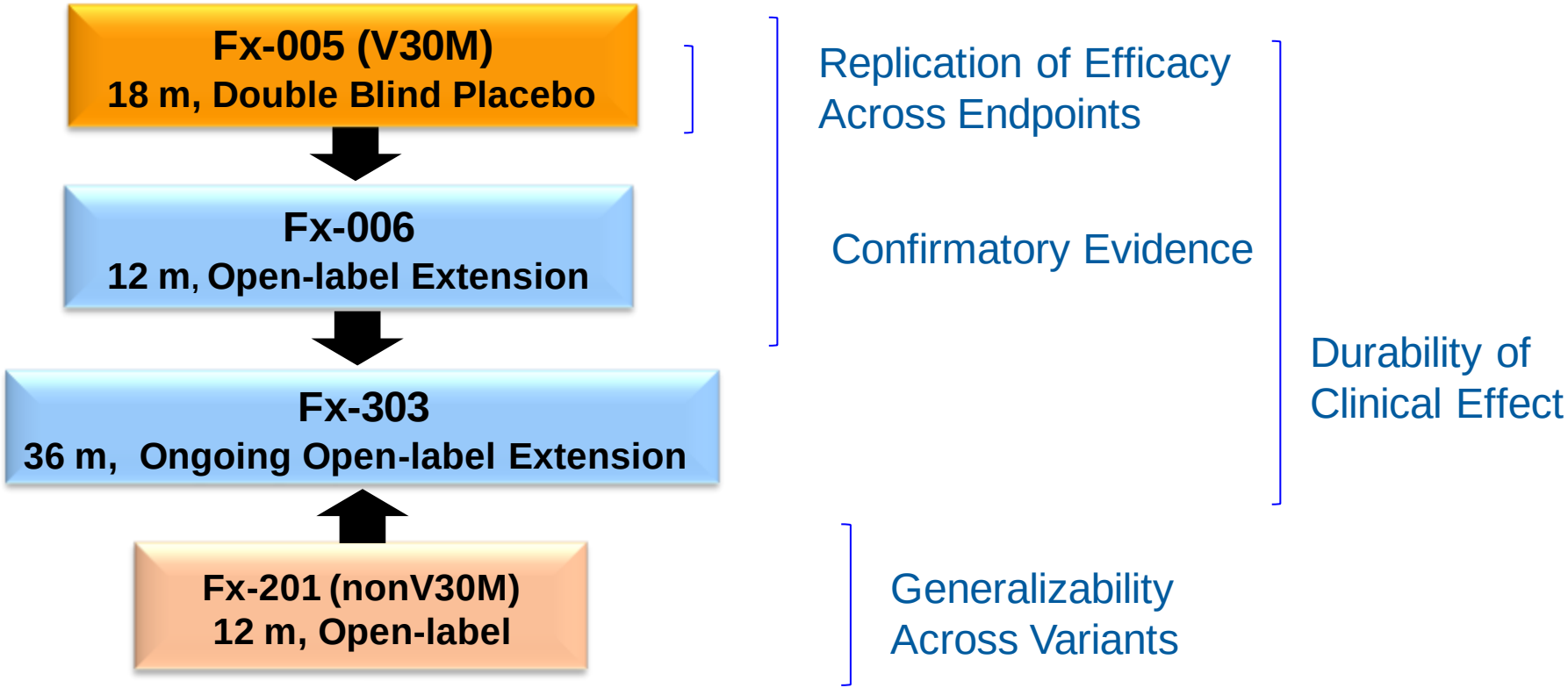


Replication of Efficacy
Across Endpoints

Confirmatory Evidence

Generalizability
Across Variants

Core Clinical Program



Totality of Data Supports Approval of Tafamidis in TTR-FAP

- 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

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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

Ando 2005

- 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

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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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

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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?

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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

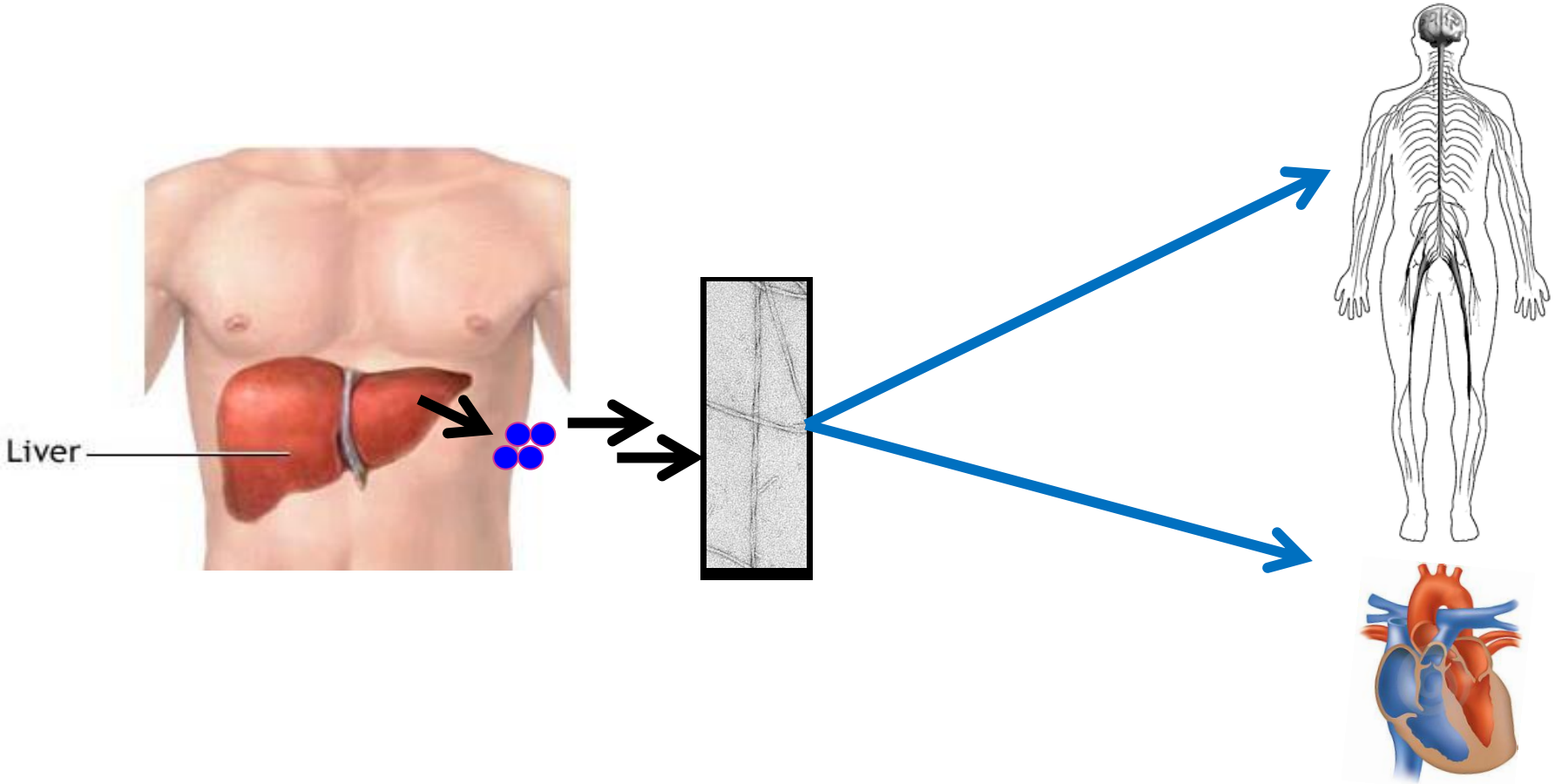
Tafamidis Mechanism of Action and Dose Selection

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

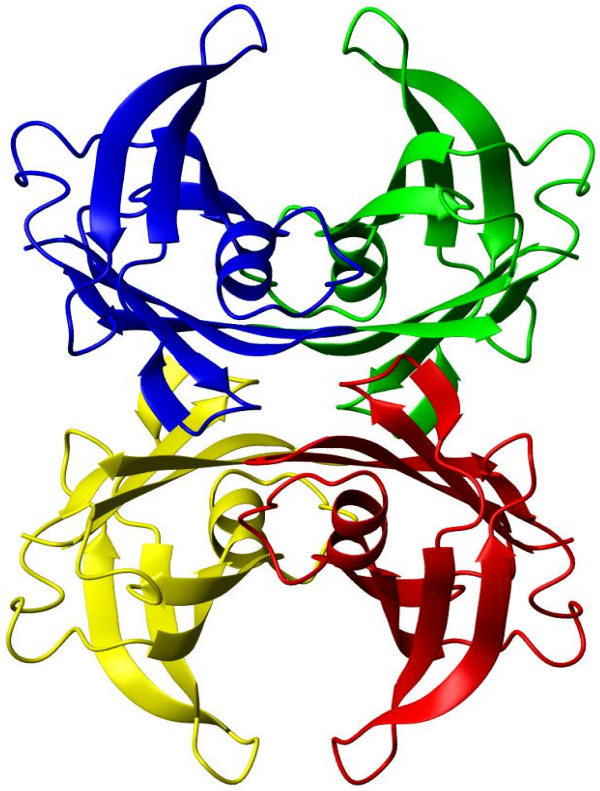
Outline of Today's Talk

- 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)

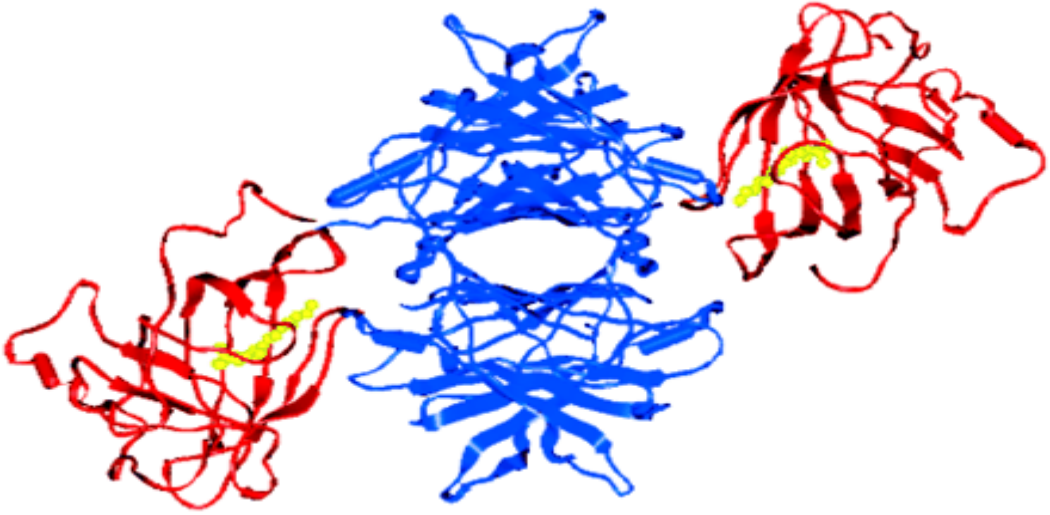
Transthyretin (TTR) Aggregation Leads to the Demise of Post-mitotic Tissue



Transthyretin–Prominent Plasma Protein Retinol Binding Protein Carrier

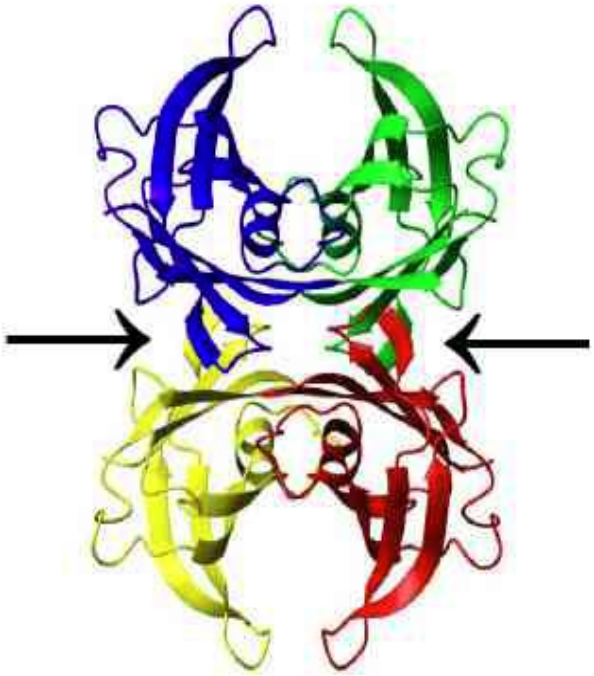


127AA β-sheet rich 55 kDa homotetramer



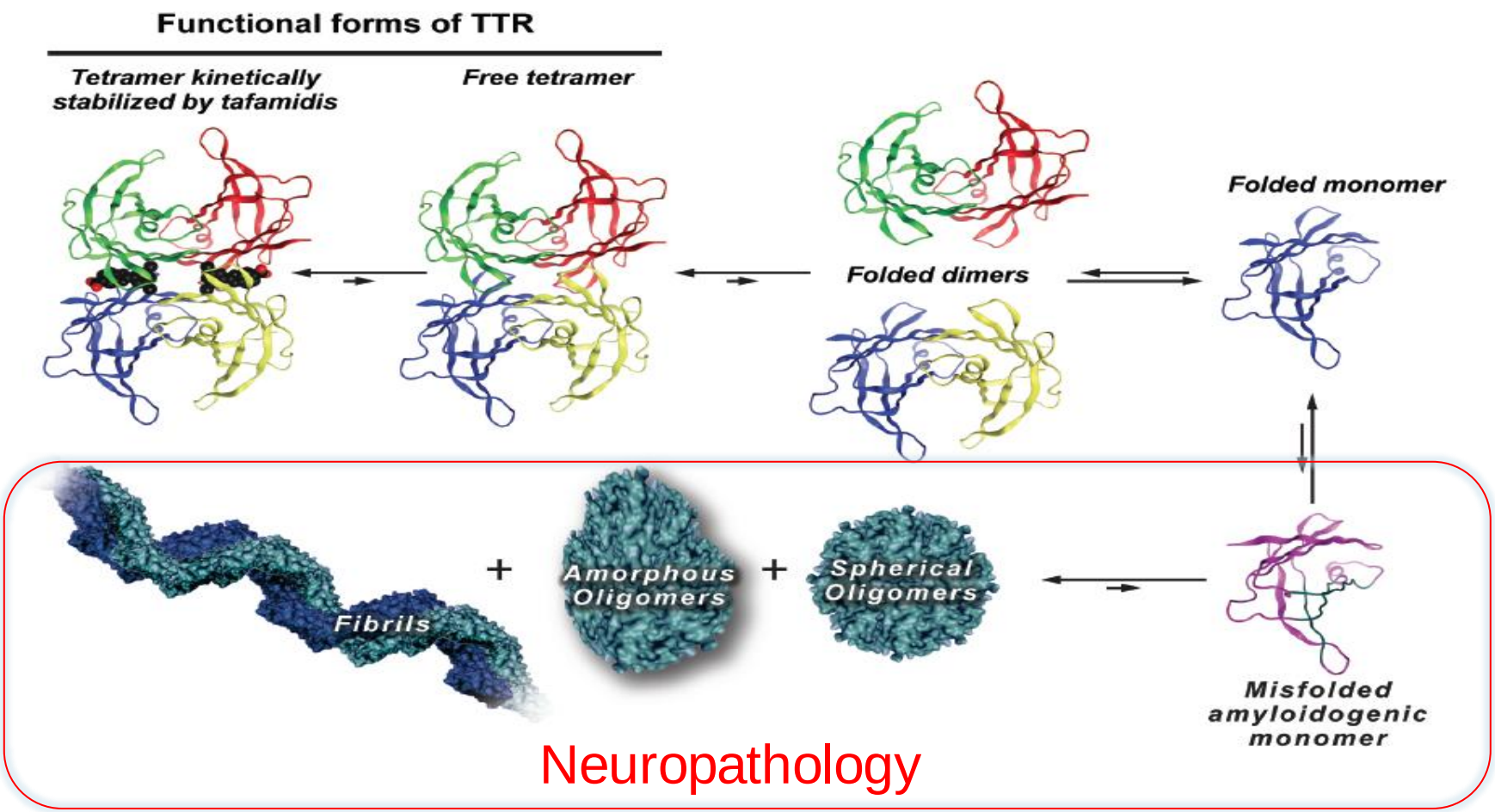
TTR-$(RBP)_2$

Human Transthyretin is a Backup Thyroid Carrier

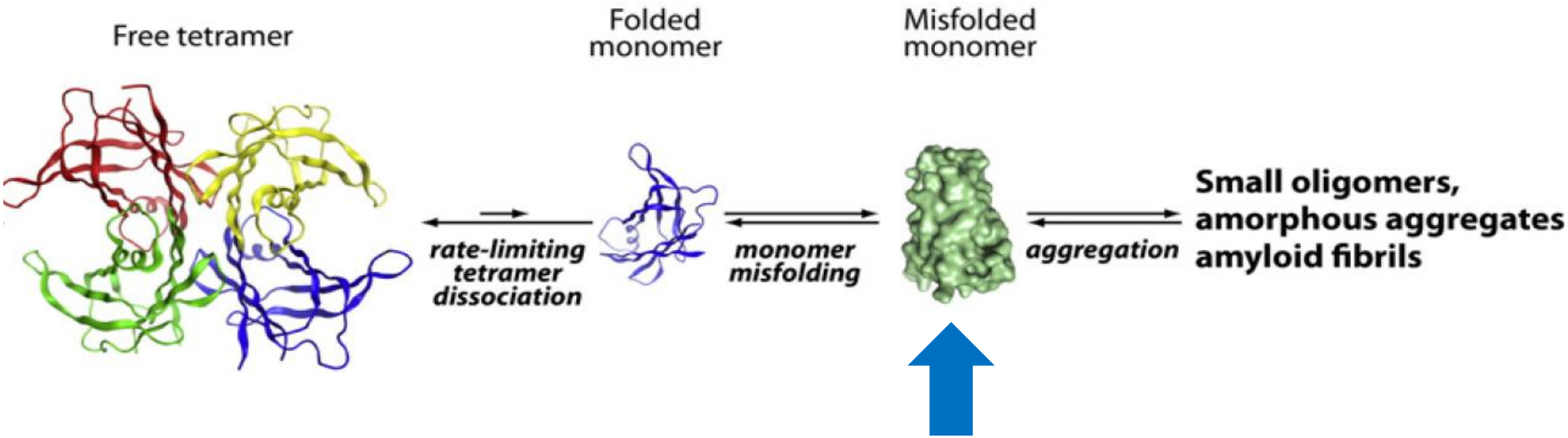


<1% of TTR bound to T_4

Rate Limiting Tetramer Dissociation & Monomer Misfolding Leads to Aggregation



All TTR Disease Variants Are Destabilized



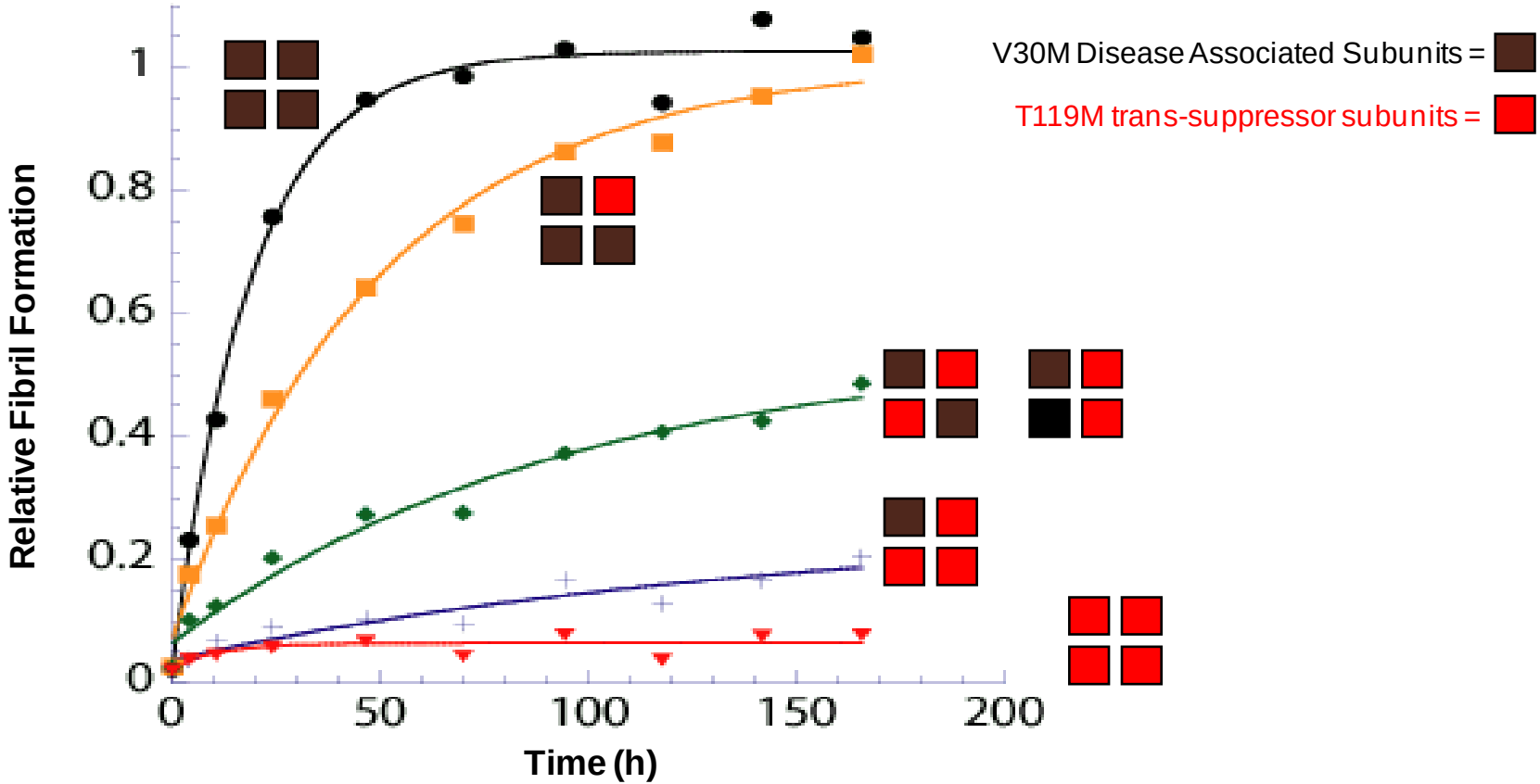
Pathological mutations destabilize the tetramer leading to higher concentration of the amyloidogenic monomer

Biochemistry 1993, *32*, 12119-12127, Biochemistry, 1995, 34, 13527-13536,
Proc. Natl. Acad. Sci. 2002, 99, 16427-16432, *Cell* 2005 121, 73-85.

A Key Observation From Dr. Teresa Coelho

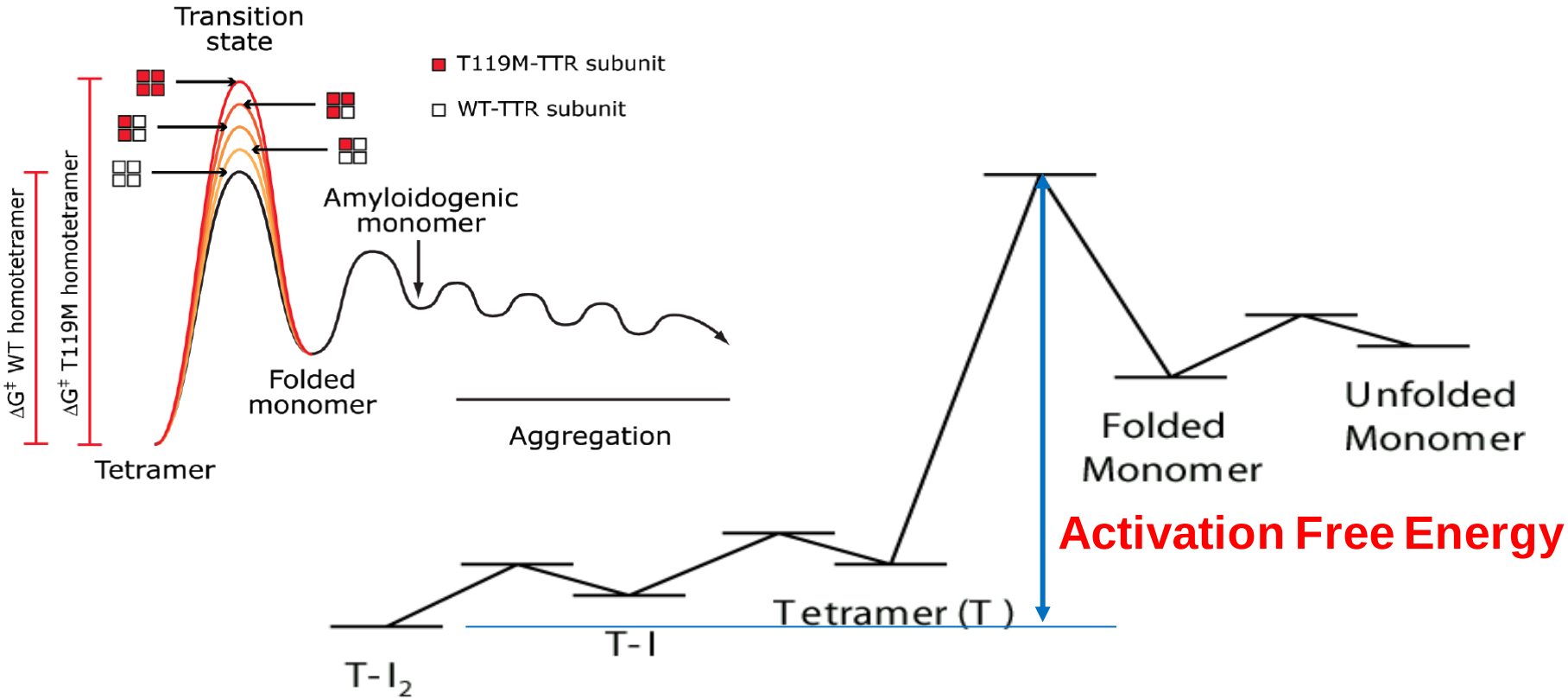
- V30M TTR-FAP highly penetrant in Portugal
- Families with V30M mutation exhibit a benign course of TTR-FAP
- These individuals have a second mutation, T119M, on their second allele
- Hence their heterotetramers comprising T119M and V30M subunits appear to be less amyloidogenic – Interallelic trans-suppression

A T119M/V30M Compound Heterozygous Family Reveals That Interallelic Trans–Suppression Ameliorates Pathology



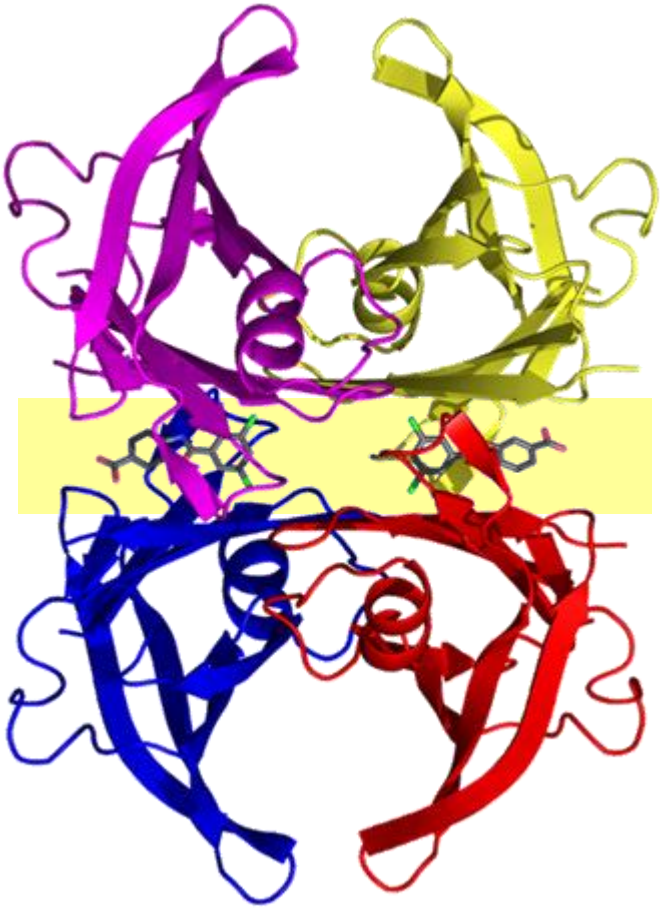
Hammarstrom et al.*Science* 2001, 293, 2459-2461;*Science* 2003, 299, 713-716.

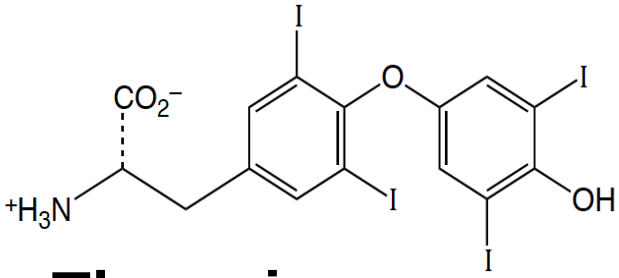
Native State Kinetic Stabilization Mediated by Activation Barrier Tuning with Small Molecules



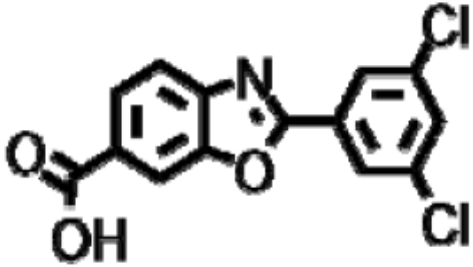
Hammarstrom et al. *Science* 2003, 299, 713-716; Razavi, Powers et al. *Angew. Chem. Int. Ed.* 2003, 42, 2758-2761; Johnson. *Acct. Chem. Res.* 2005, 38, 911-921.

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



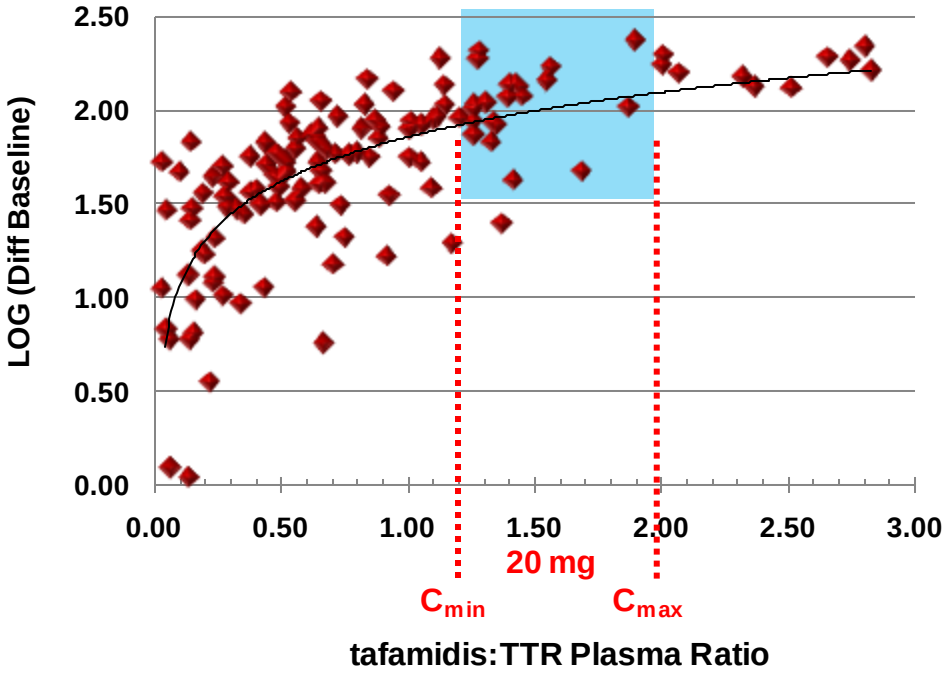


Thyroxine



Tafamidis K_{d1} **= 2 nM;**
K_{d2} **= 154 nM**

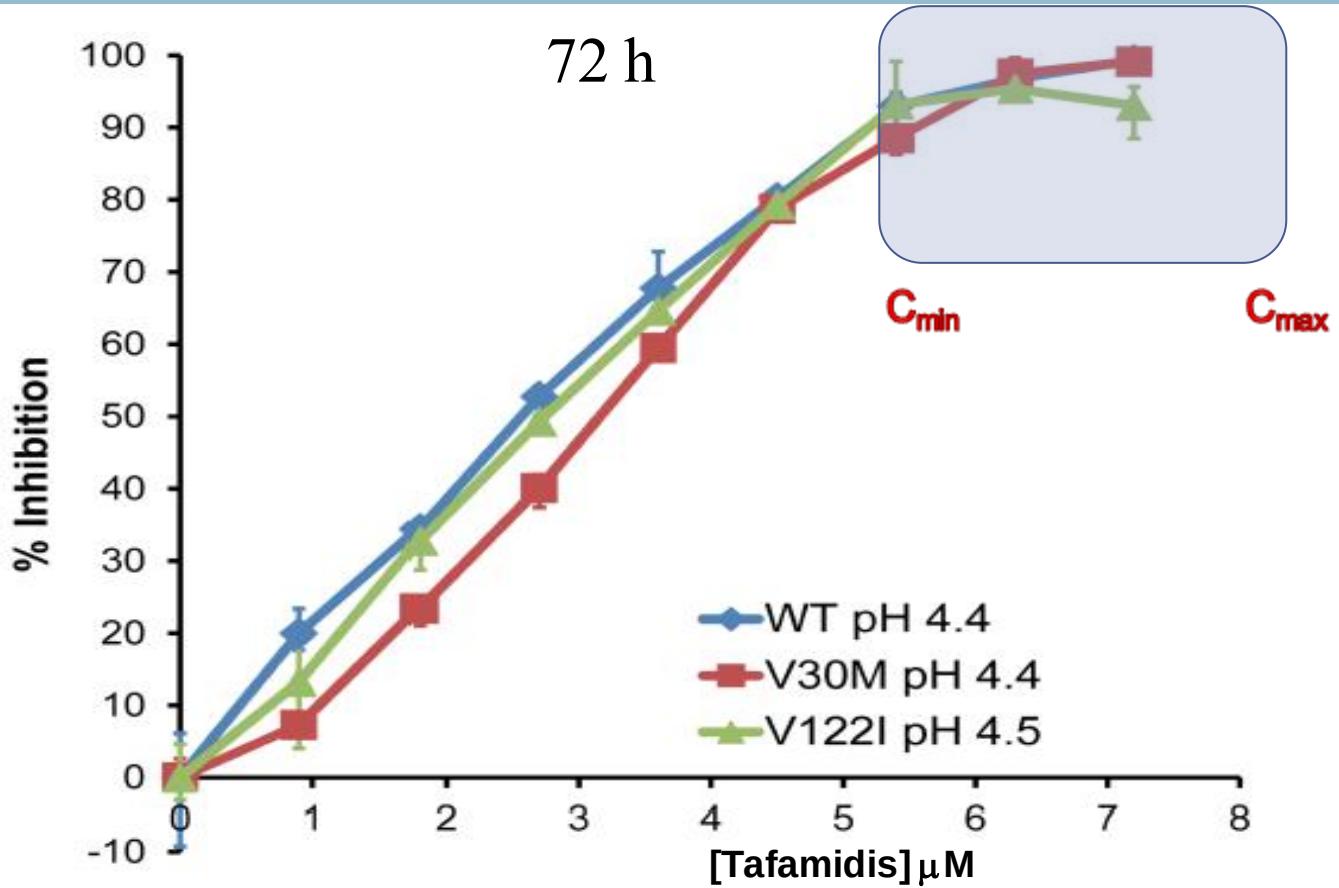
Demonstrating Transthyretin Tetramer Stabilization & Amyloid Inhibition at 20 mg Once a Day



- Dose selection based on PK/PD
- At 20 mg steady state:
  - Plasma concentration over 1000x > Kd
  - C_{min} = 5.2 uM; C_{max} = 8.4 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



Bulawa, C.E.; Connelly, S.; DeVit, M.; Wang, L. Weigel, C.;Fleming, J. Packman, J.; Powers, E.T.; Wiseman, R.L.; Foss, T.R.; Wilson, I.A.; Kelly, J.W.; Labaudiniere, R. Proc. Natl. Acad. Sci. 2012 in press

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

Dyck 1987; Dyck 1997: Dyck 2005

Summated (Σ) Scores of Neurophysiologic Function

Σ7 – Primarily Large Fiber	Σ3 – Small fiber
Vibration detection threshold	Cooling detection threshold
Heart rate variability with deep respiration	Heat pain
Nerve conduction studies Peroneal nerve Tibial nerve Sural nerve	Heart rate variability with deep respiration

Dyck 1987; Dyck 1997: Dyck 2005; Kim 2009

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

*Vinik Diab Tech Thera 2005; Vinik Clin Ther 2005; Vinik J Diab Sci Tech 2008

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 x serum albumin (g/L)

Suhr 1994; Suhr 2002; Suhr 2005

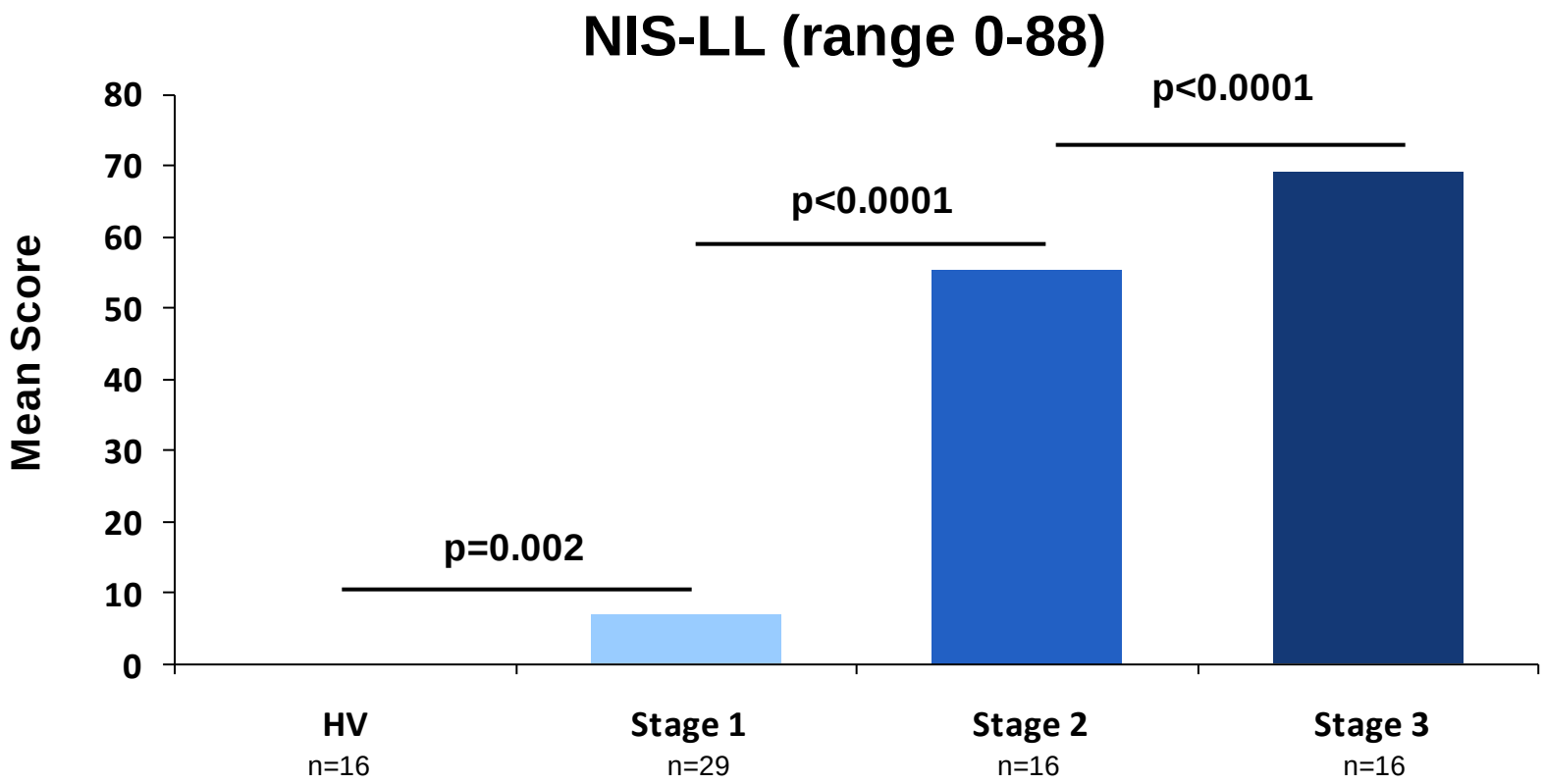
How Applicable Are Measures To TTR-FAP? Fx1A-OS-001 Study

- **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

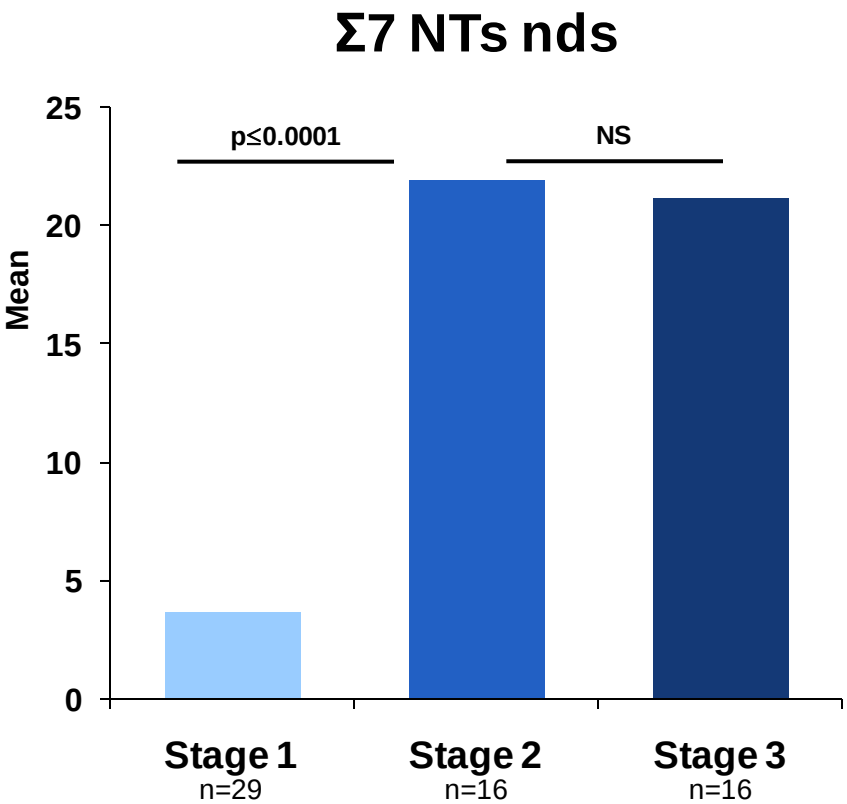
* Stages According to: Coutinho in *Amyloid and amyloidosis*. Amsterdam. 1980; 88-98

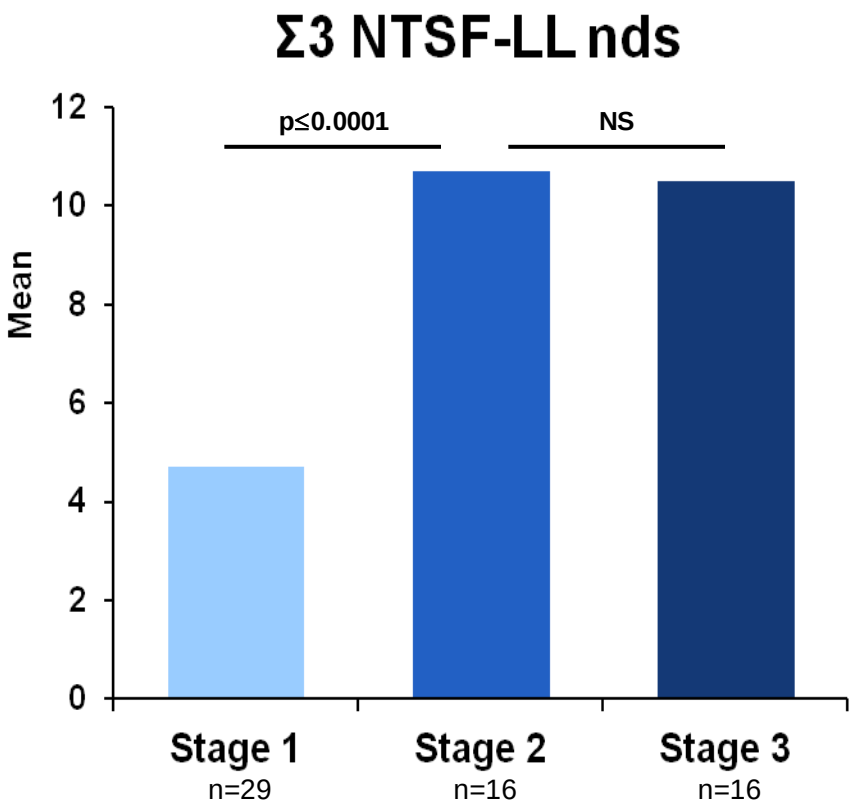
NIS-LL Discriminates Across TTR-FAP Stages



Study Fx1A-OS-001
HV = healthy volunteers
Pairwise p-values based on an analysis of variance without adjustment for multiple testing

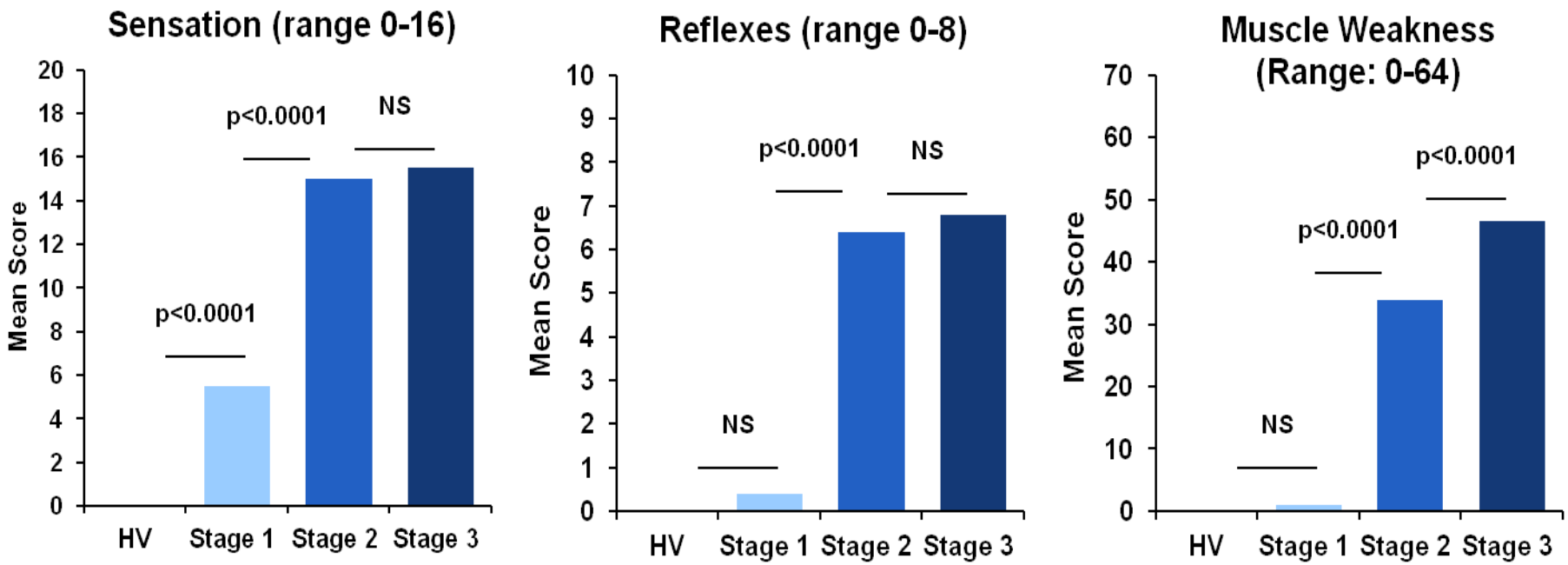
Neurophysiological Assessments





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



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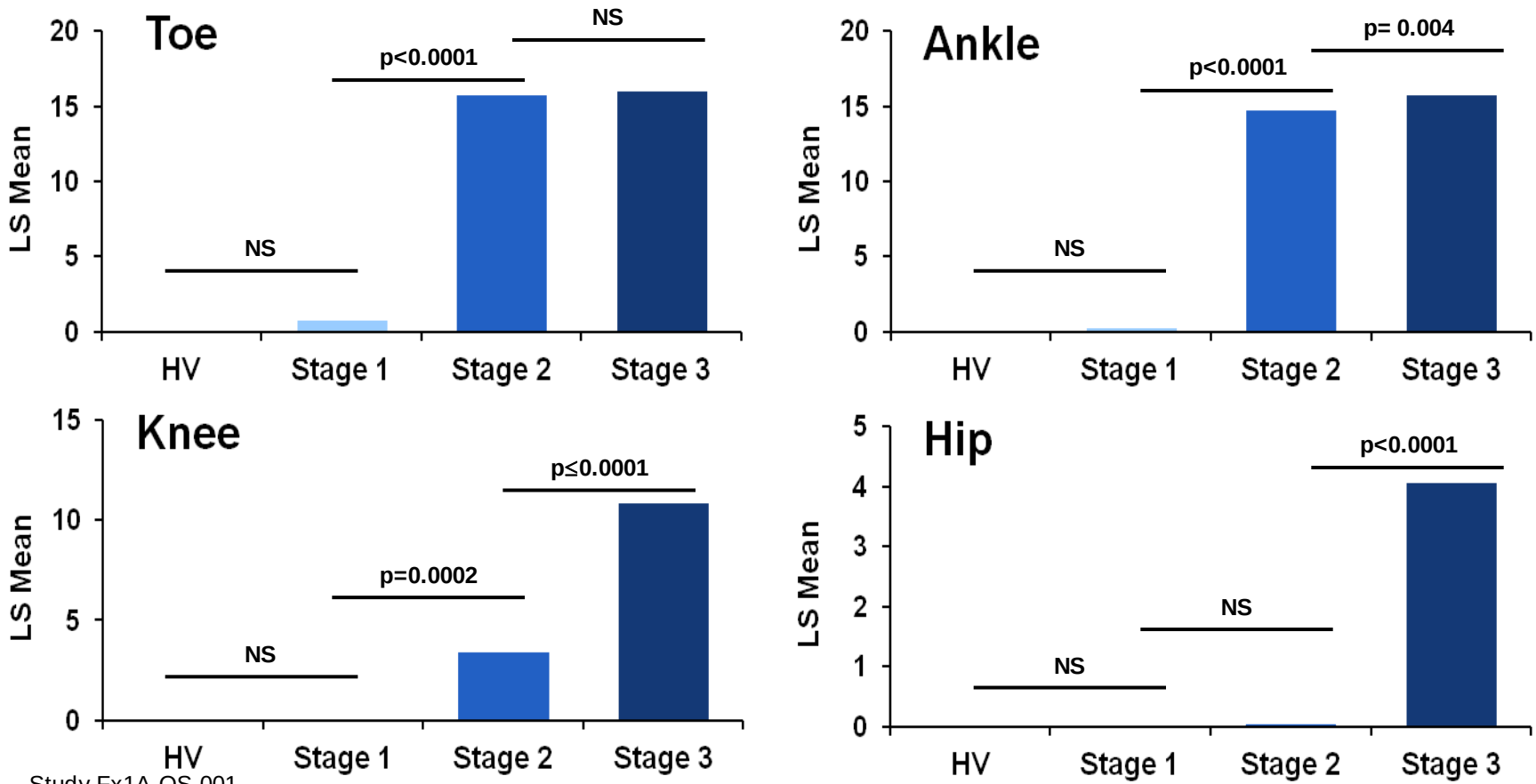
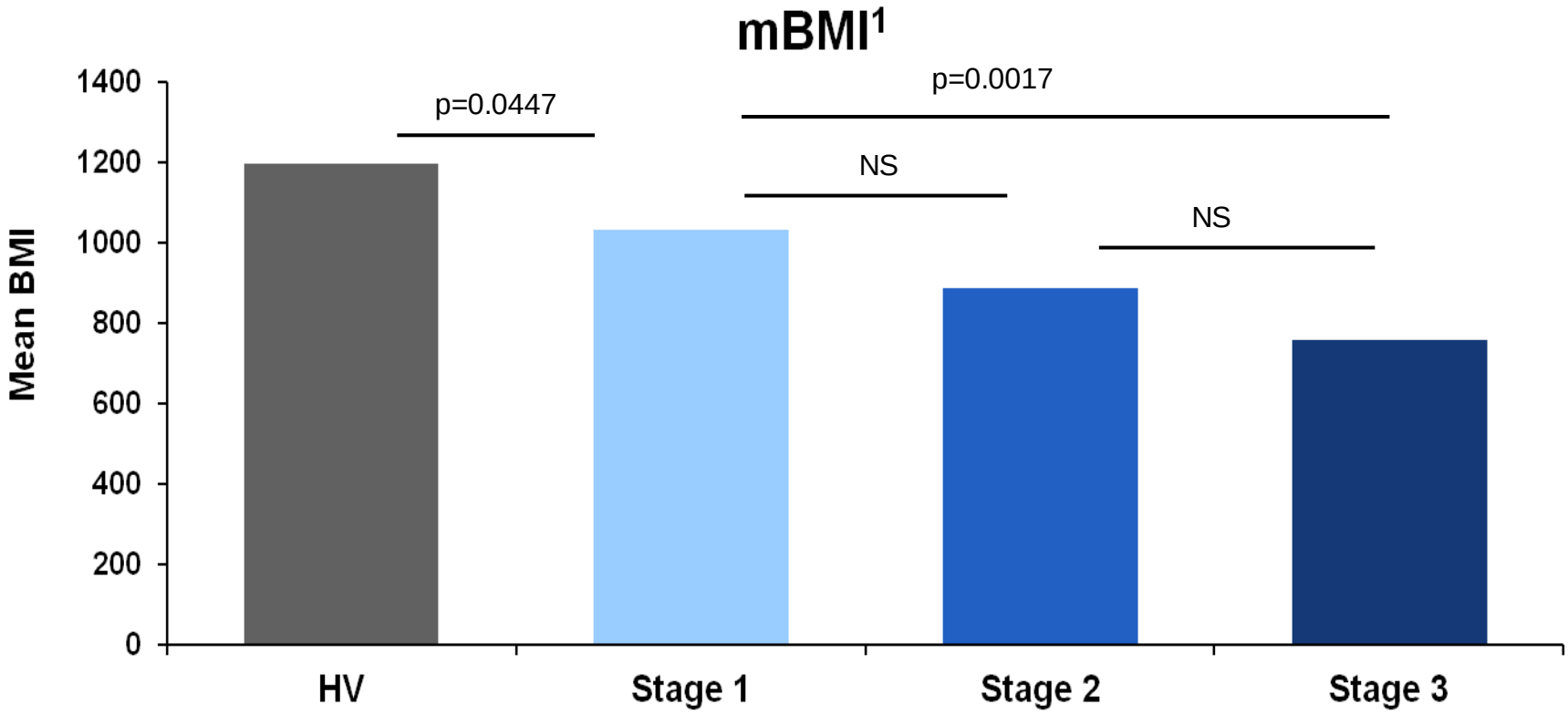
Muscle Weakness Progresses from Distal to Proximal



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

Modified Body Mass Index Decreases with Disease Stage



NS=Not significant, p-value> 0.05
Pairwise comparisons without adjustment for multiple testing.

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

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

Presentation Outline

Development Program Overview

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

Tafamidis TTR-FAP Development Program

Study Fx-005	
18-month, randomized double-blind, placebo-controlled study	Pivotal study in V30M patients with TTR-FAP

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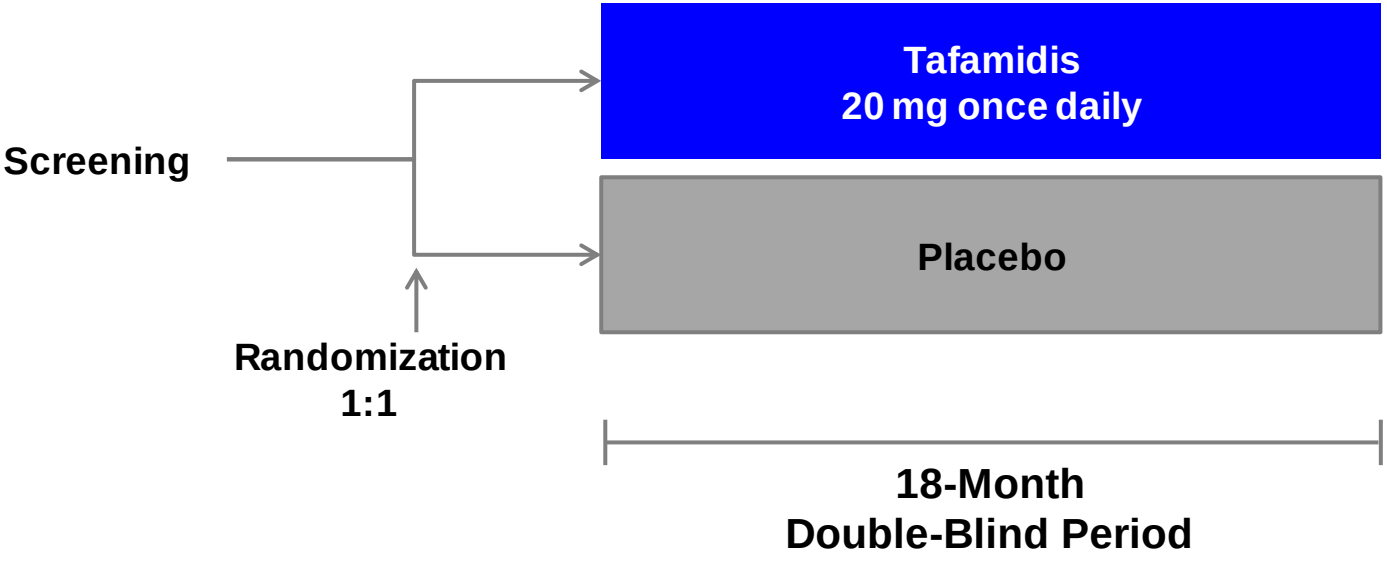
Study Fx-006	
12-month, open-label extension for Fx-005	Long-term safety and efficacy

Study Fx1A-303	
Open-label, multicenter, 36-month study	Long-term extension study for Fx-006 and Fx1A-201 (study is ongoing)

Overview of Pivotal Study Fx-005



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

Primary and Key Secondary Endpoint
Fx-005

- 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^

TQOL= Total Quality of Life Score from Norfolk QOL-DN
* Chi square test of proportions
+ ANCOVA with baseline as covariate
^MMRM (Mixed Model Repeated Measures)

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

Reasons not included in ITT	Tafamidis n=65	Placebo n=63
Negative genotype		1
AE (no post-baseline evaluation)	1	1

ITT population
n=125

Reasons not included in ITT	Tafamidis n=64	Placebo n=61
Liver transplantation	13	13
AE / Pregnancy	3	2
Withdrew consent	1	2

Completed 18 Months
n=91

Reasons not included in EE population	Tafamidis n=47	Placebo n=44
Important protocol deviation	2	2

Efficacy Evaluable Population
n=87

Distribution of Randomized Patients and TTR Transplant Recipients by Study Center Country

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

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

Baseline Demographics
Fx-005 (ITT)

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

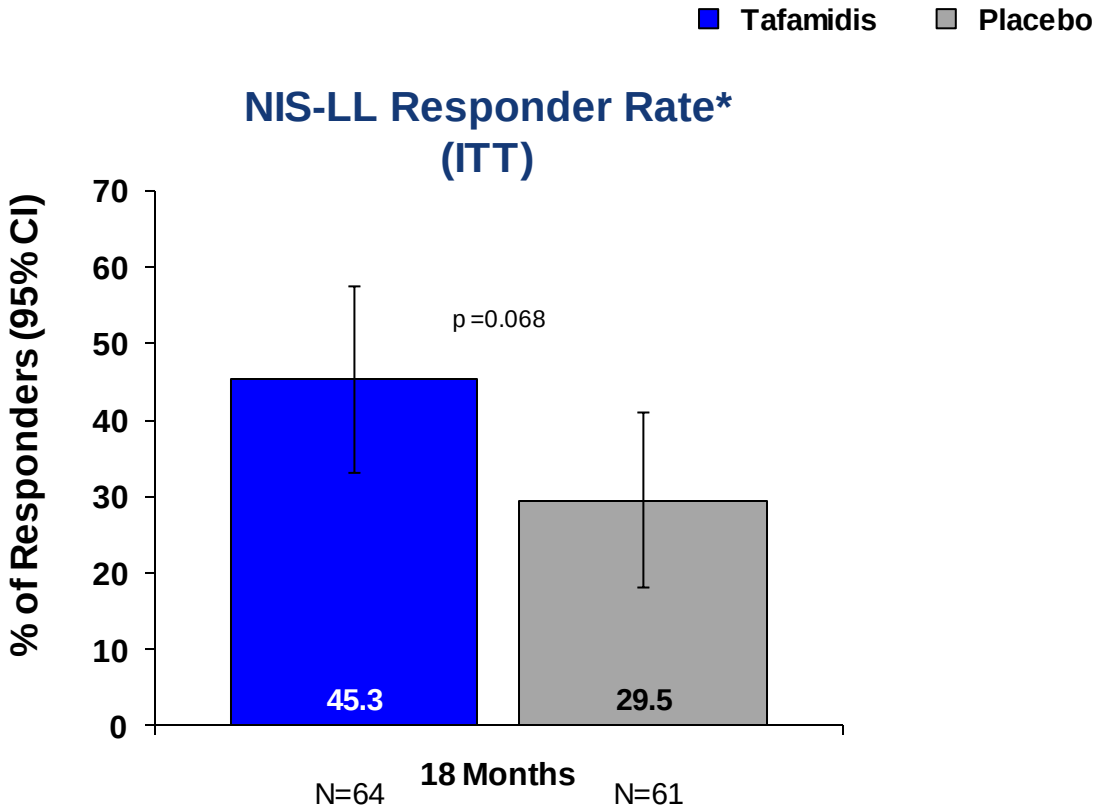
* Continuous variable p-value based on Wilcoxon Rank Sum test; Categorical variables p-value based on a Chi-square test

Baseline Disease Characteristics
Fx-005 (ITT)

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

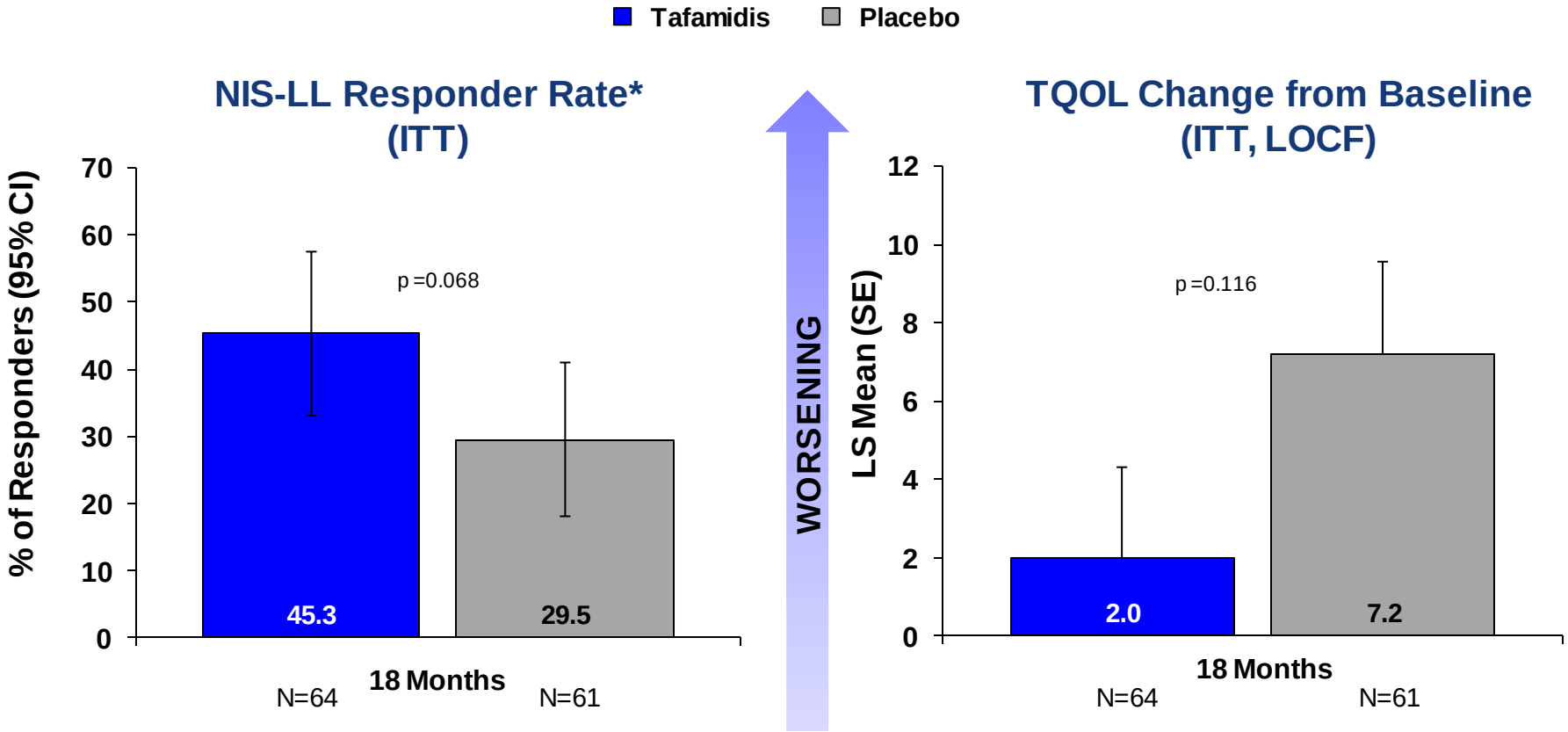
* p-values based on Wilcoxon Rank Sum test

Co-Primary Endpoints
Fx-005



* 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



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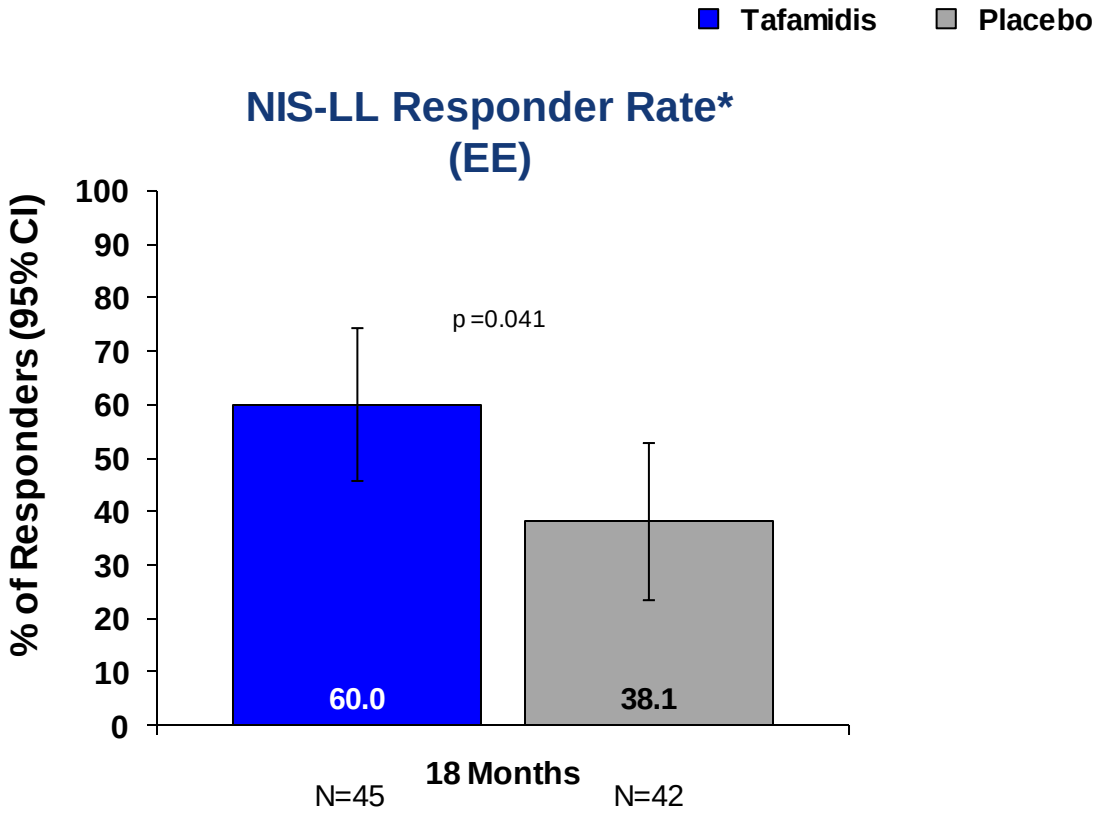
Co-Primary Endpoints
Fx-005



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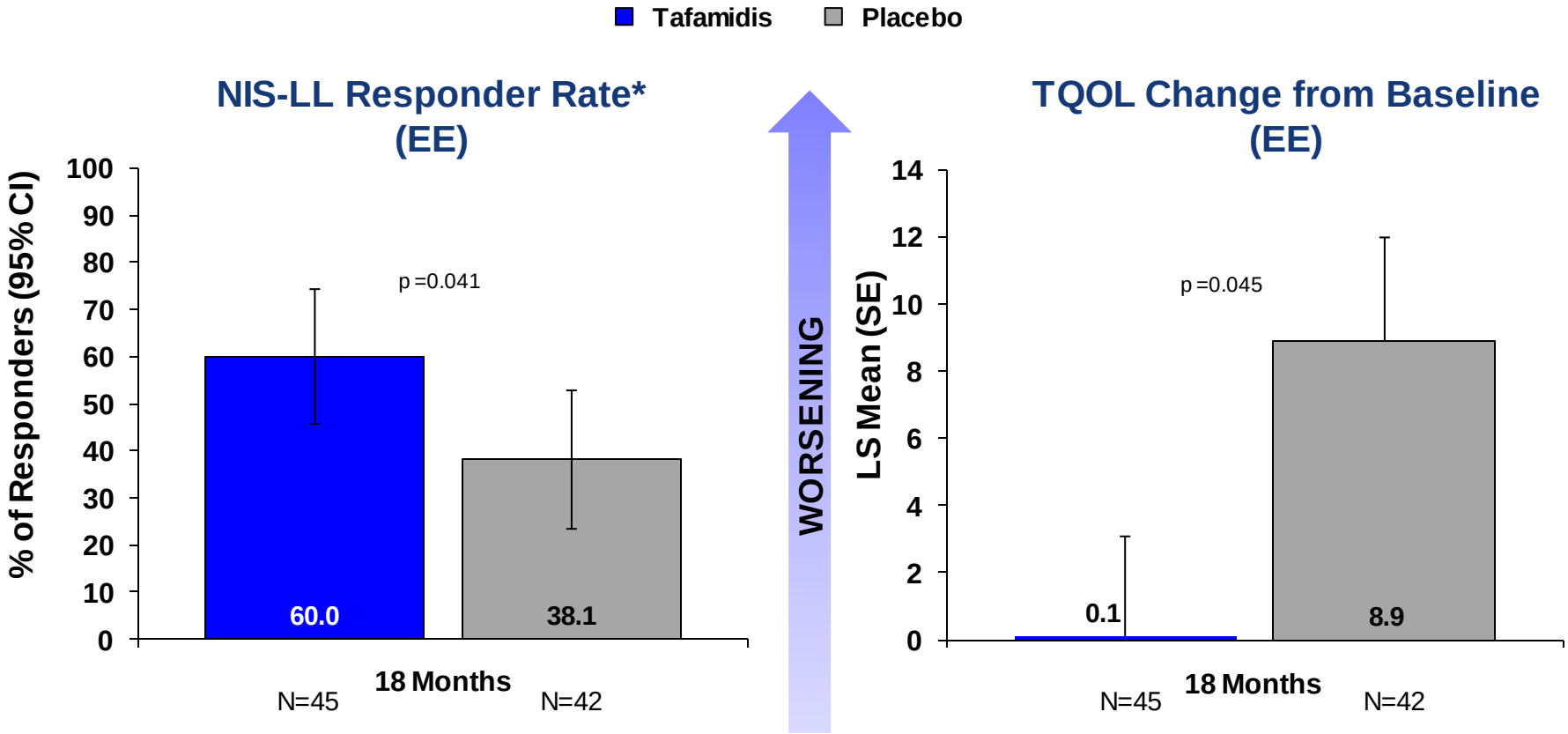

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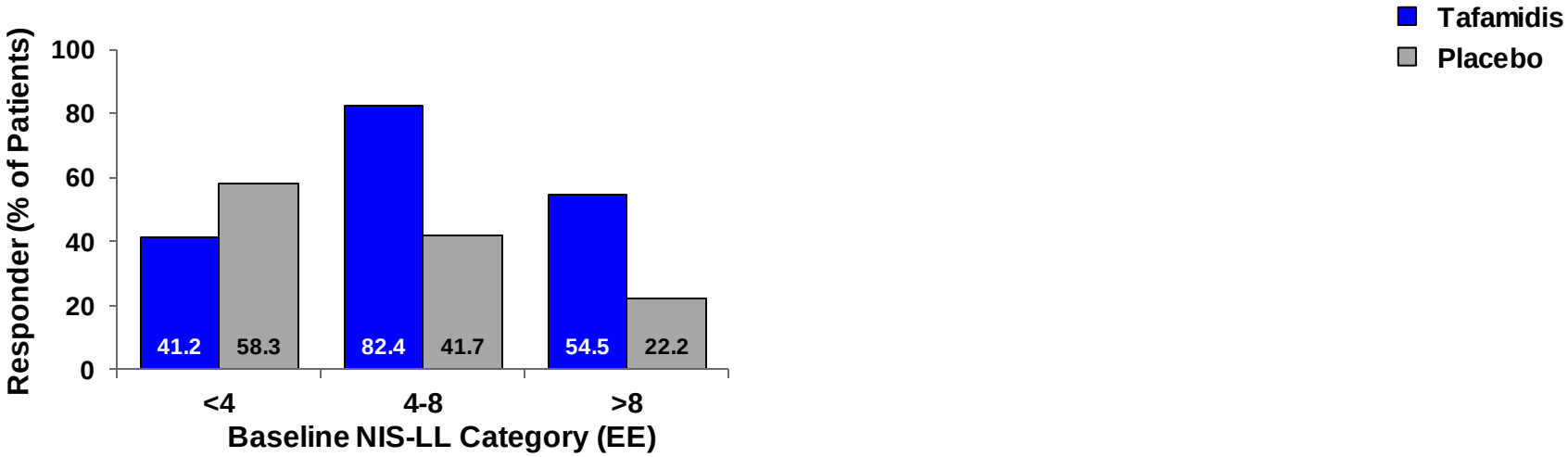
NIS-LL Responder Rate at Month 18 by Baseline Categories Fx-005



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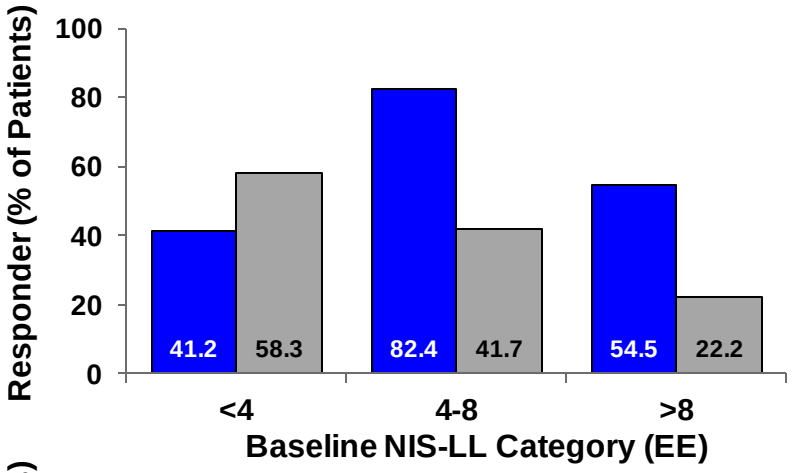

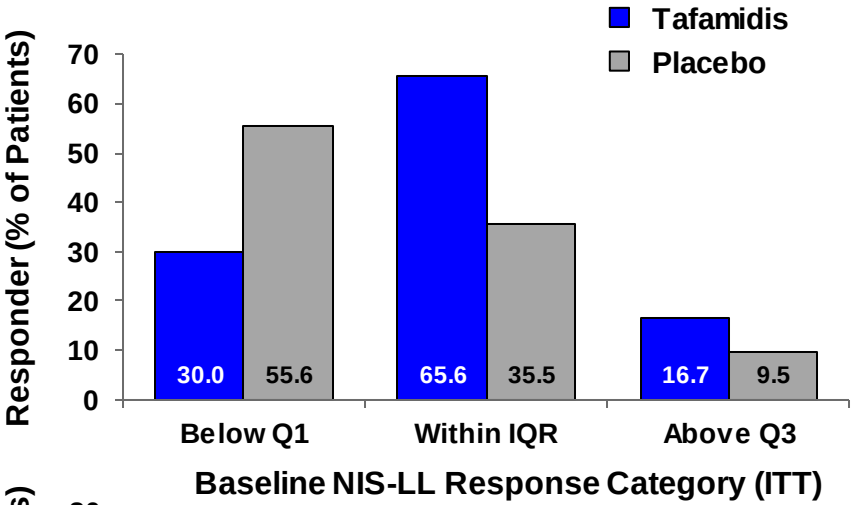

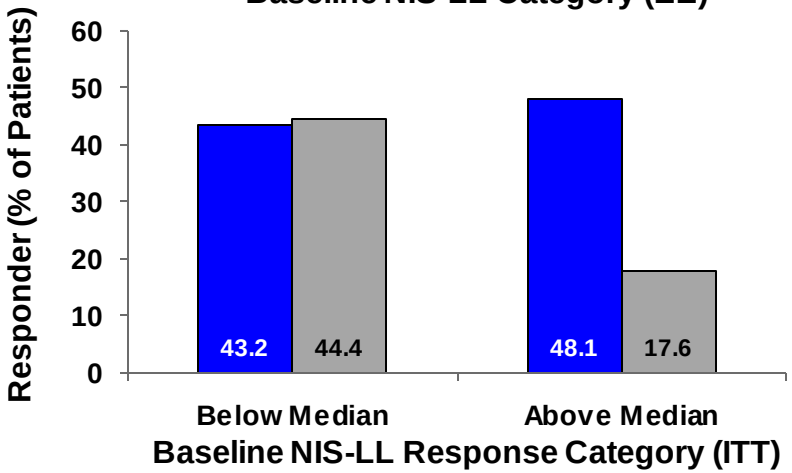

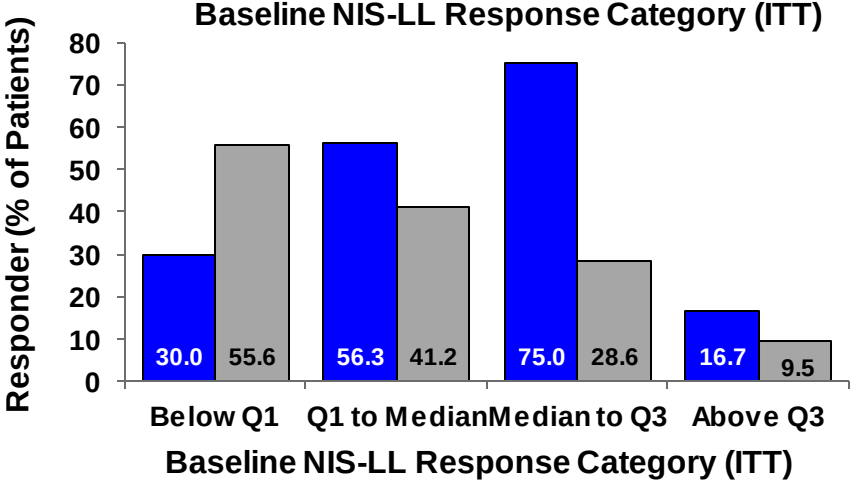

NIS-LL Responder Rate at Month 18 by Baseline Categories
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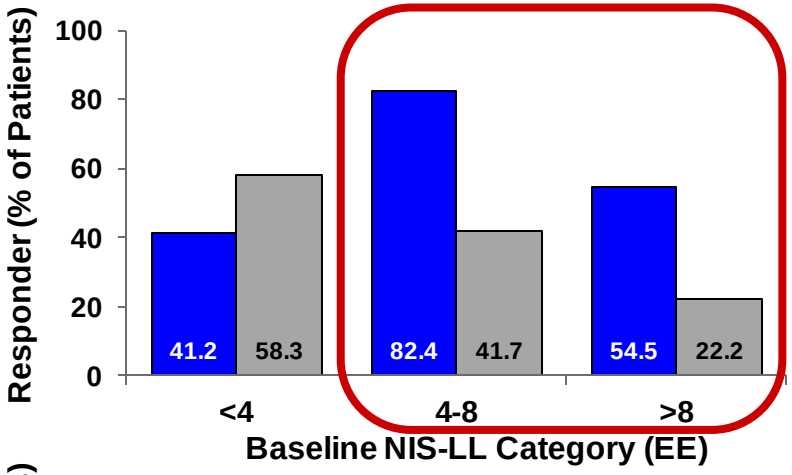
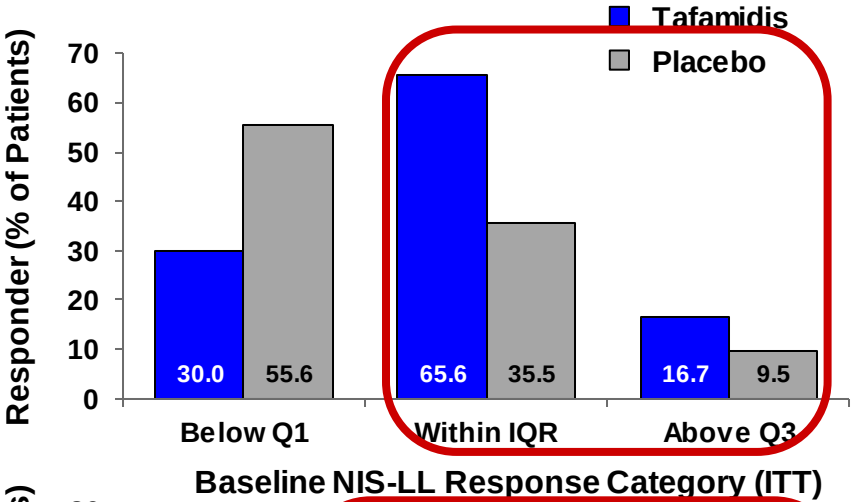
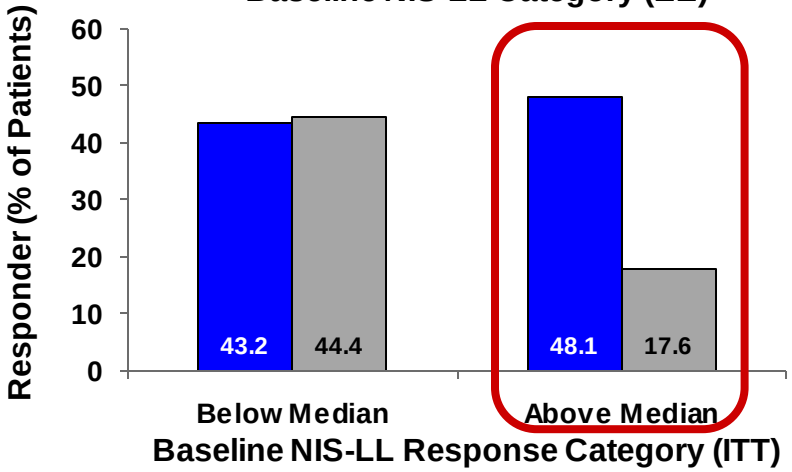
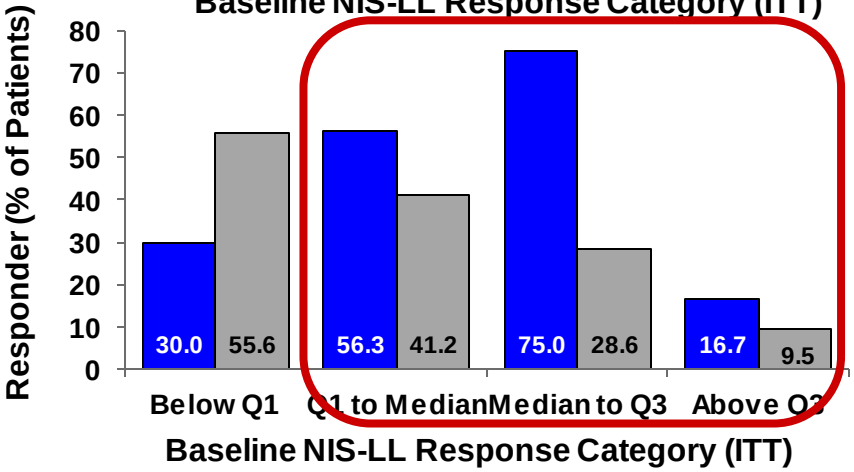
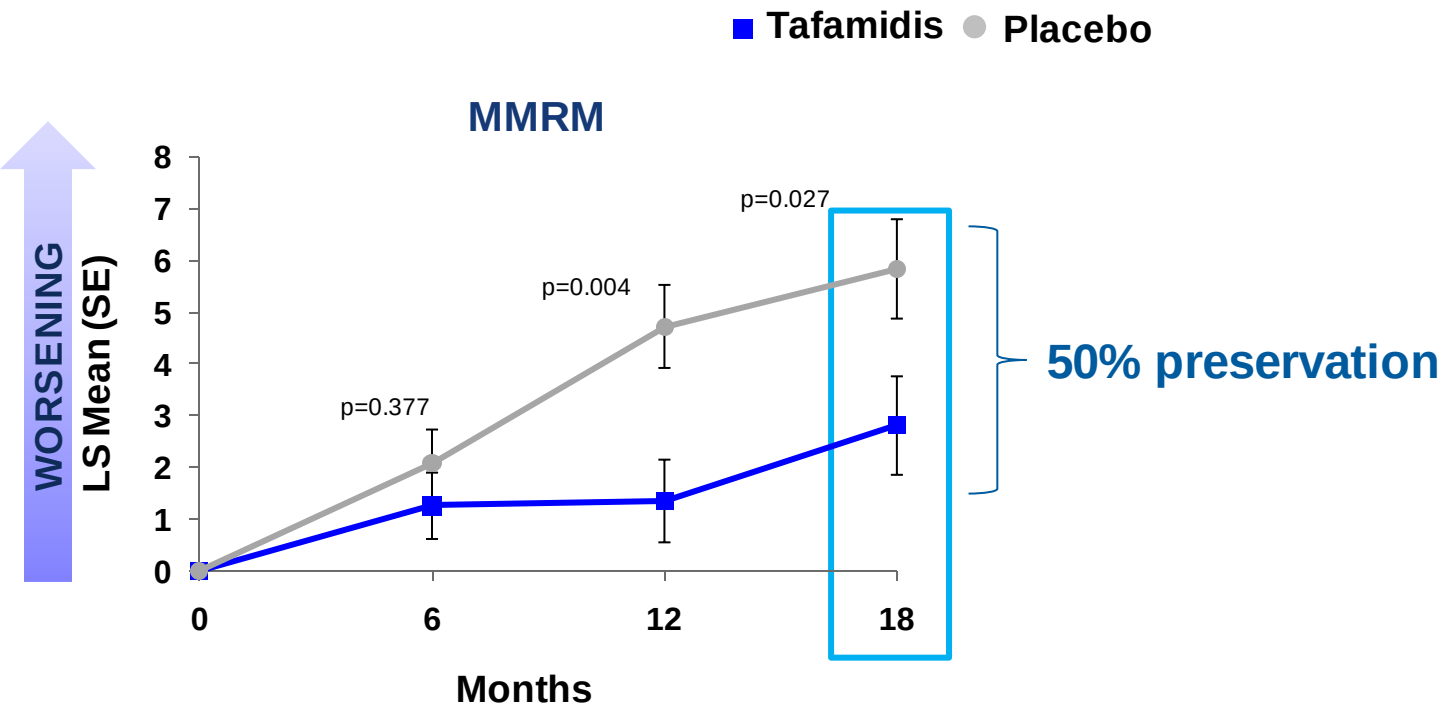








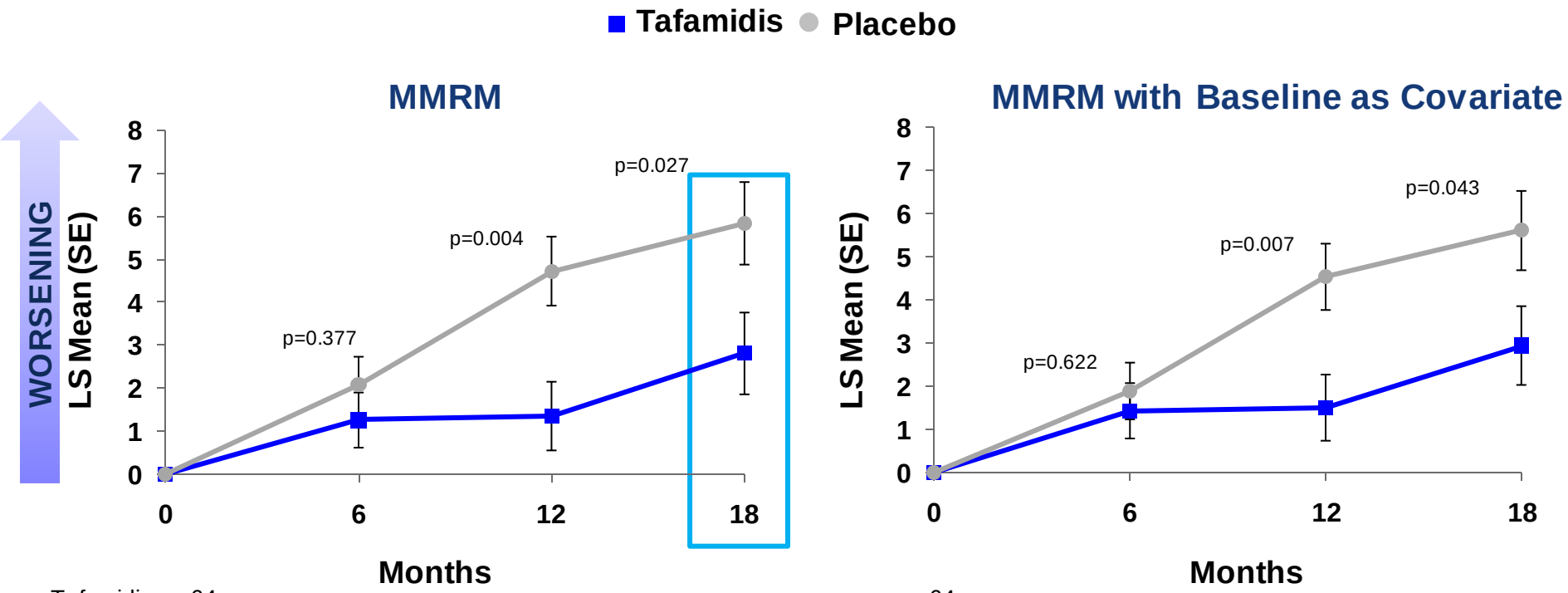
NIS-LL Change from Baseline – Mixed Model Repeated Measures (MMRM) Fx-005 (ITT, OC)



Tafamidis n=64	60	49	48
Placebo n=61	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.

NIS-LL Change from Baseline – Mixed Model Repeated Measures (MMRM) Fx-005 (ITT, OC)



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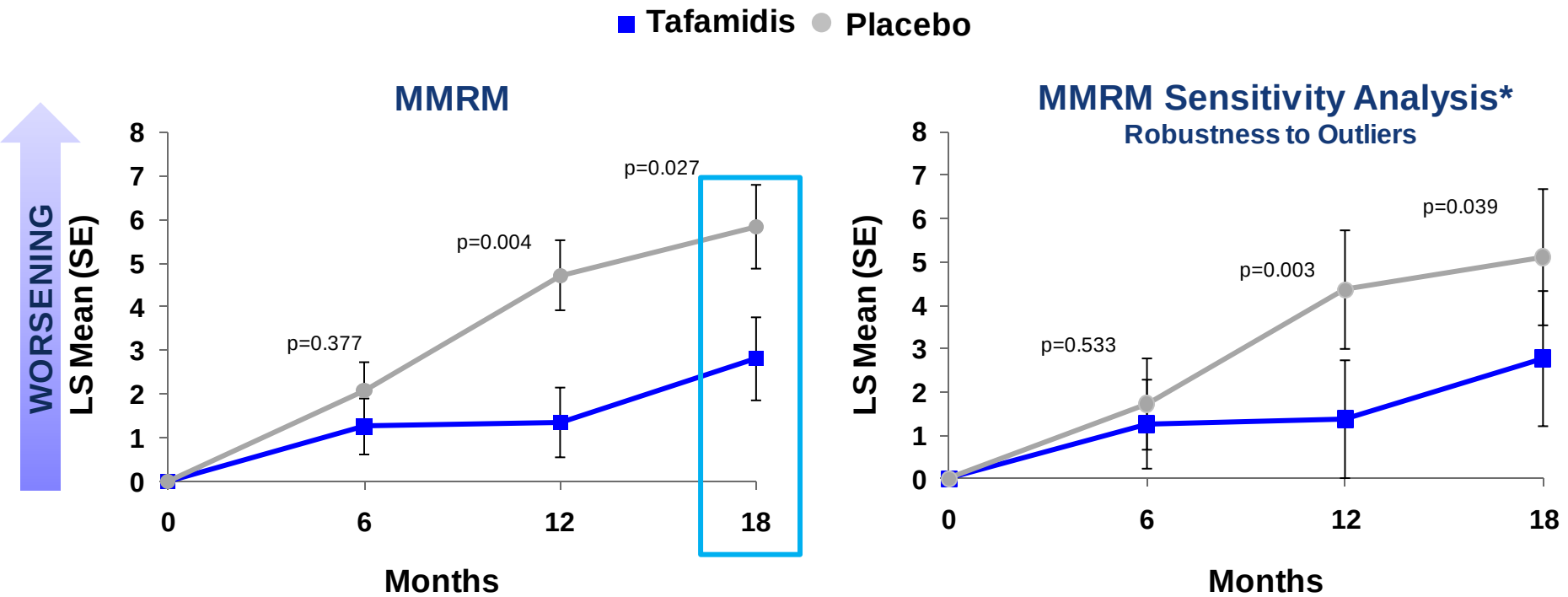
NIS-LL Change from Baseline – Mixed Model Repeated Measures (MMRM) Fx-005 (ITT, OC)



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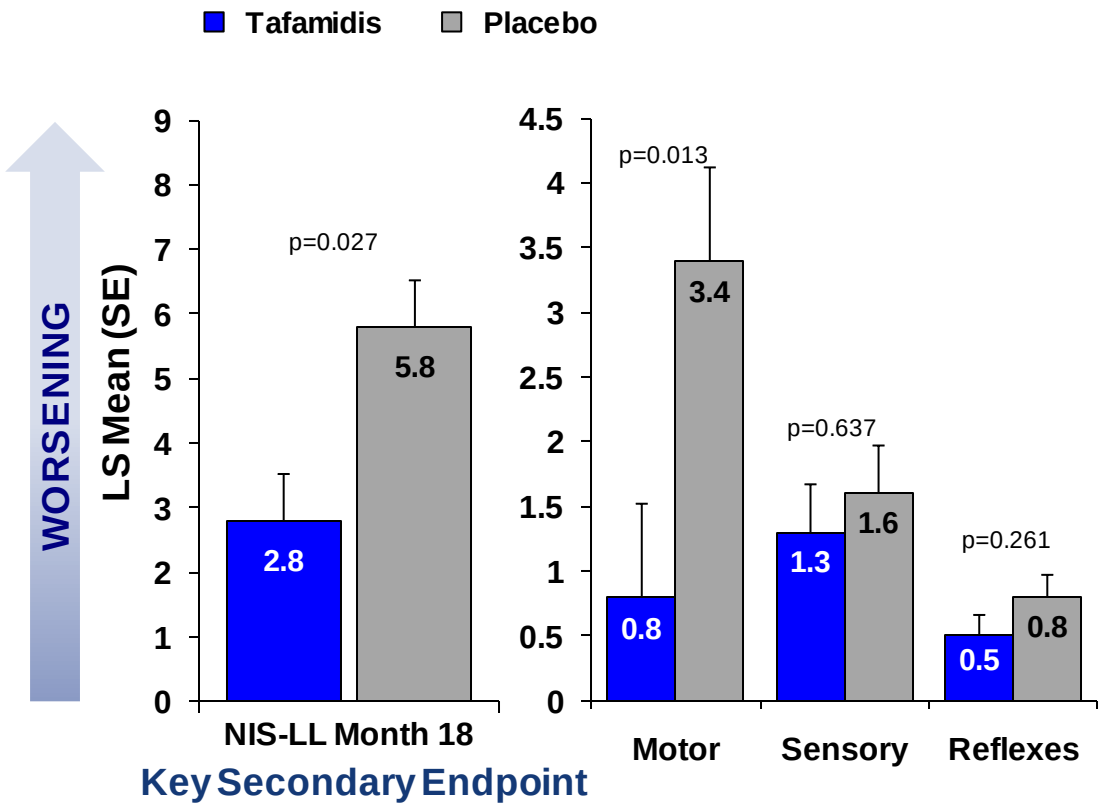
*Data from the 2 placebo patients with the highest values were replaced with data from a patient who had the third highest month 18 change value of 20

NIS-LL Change from Baseline - Statistically Significant Across Analyses and Methodologies - Fx-005 (ITT)

Analysis Method	p-value
Pre-specified Key Secondary: MMRM	0.027
MMRM with Baseline as Covariate*	0.043
MMRM Sensitivity Analysis** Robustness to outliers	0.039
Multiple Imputation*	0.041

*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)



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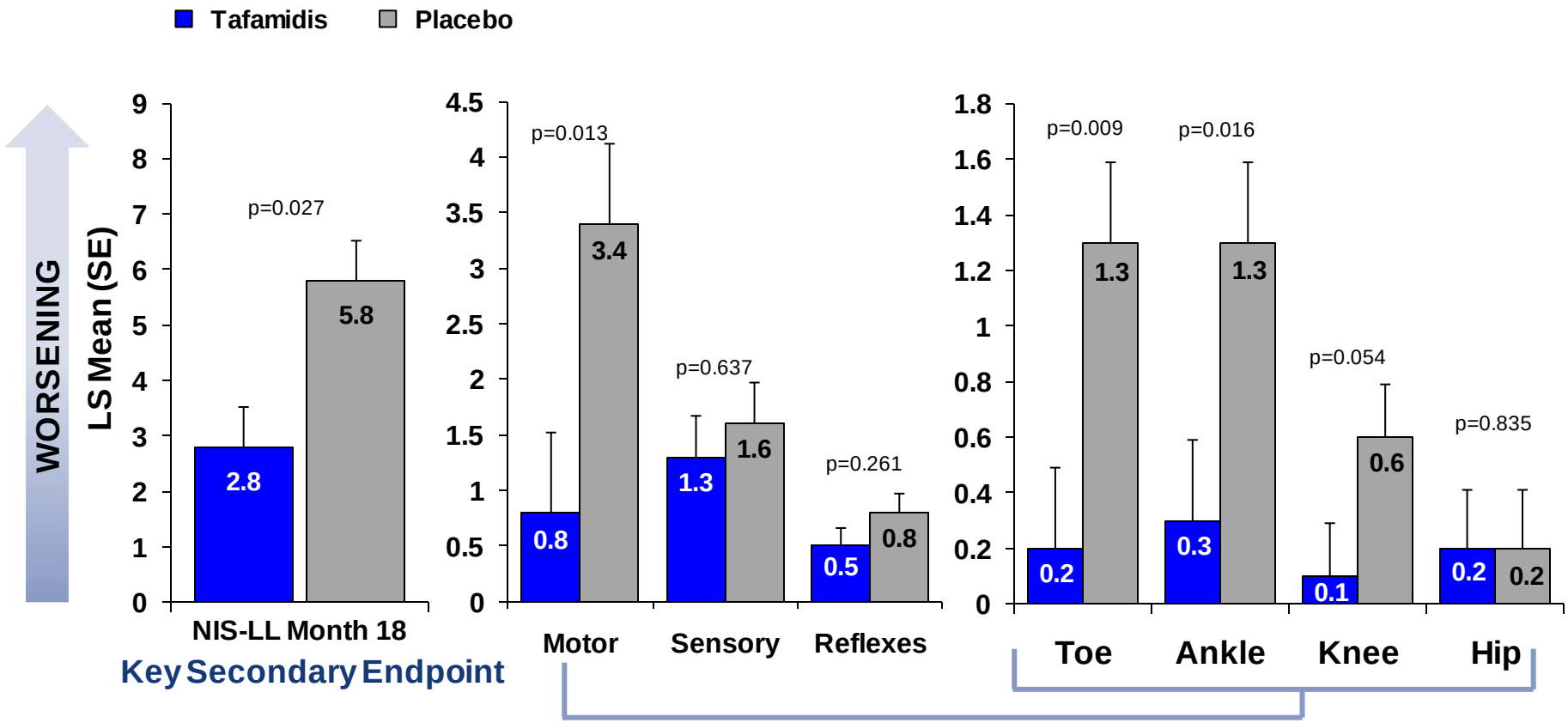
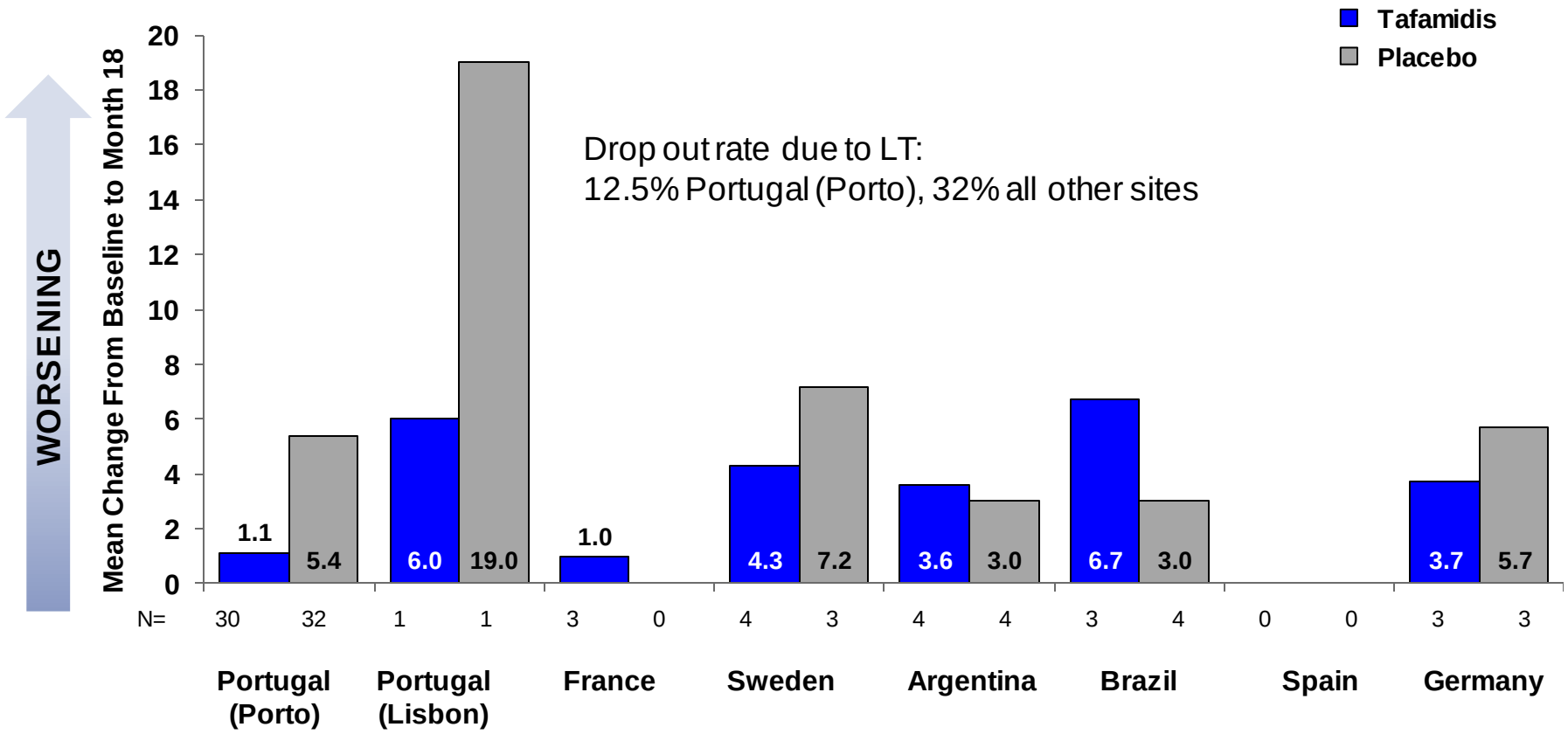
Favorable Effects of Tafamidis Primarily on NIS-LL Motor Exam
Change from Baseline to Month 18 Subscale Analysis - Fx-005 (ITT,OC)



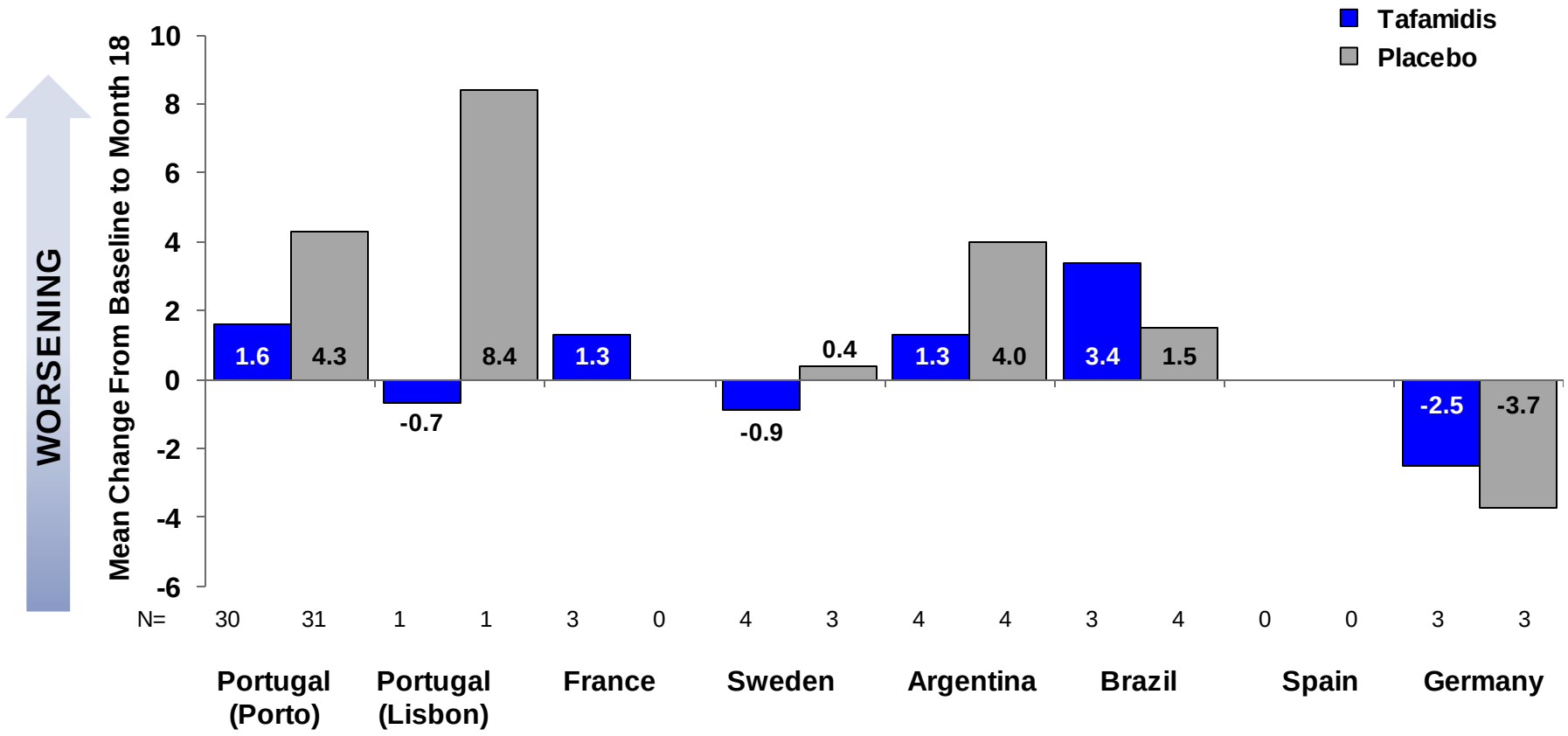
p-values are based on a model with change from baseline as the dependent variable, treatment, month and treatment x month as fixed effects, subject as a random effect, and an unstructured covariance matrix

Summary of NIS-LL Change from Baseline to Month 18 by Site Fx-005 (ITT, OC)

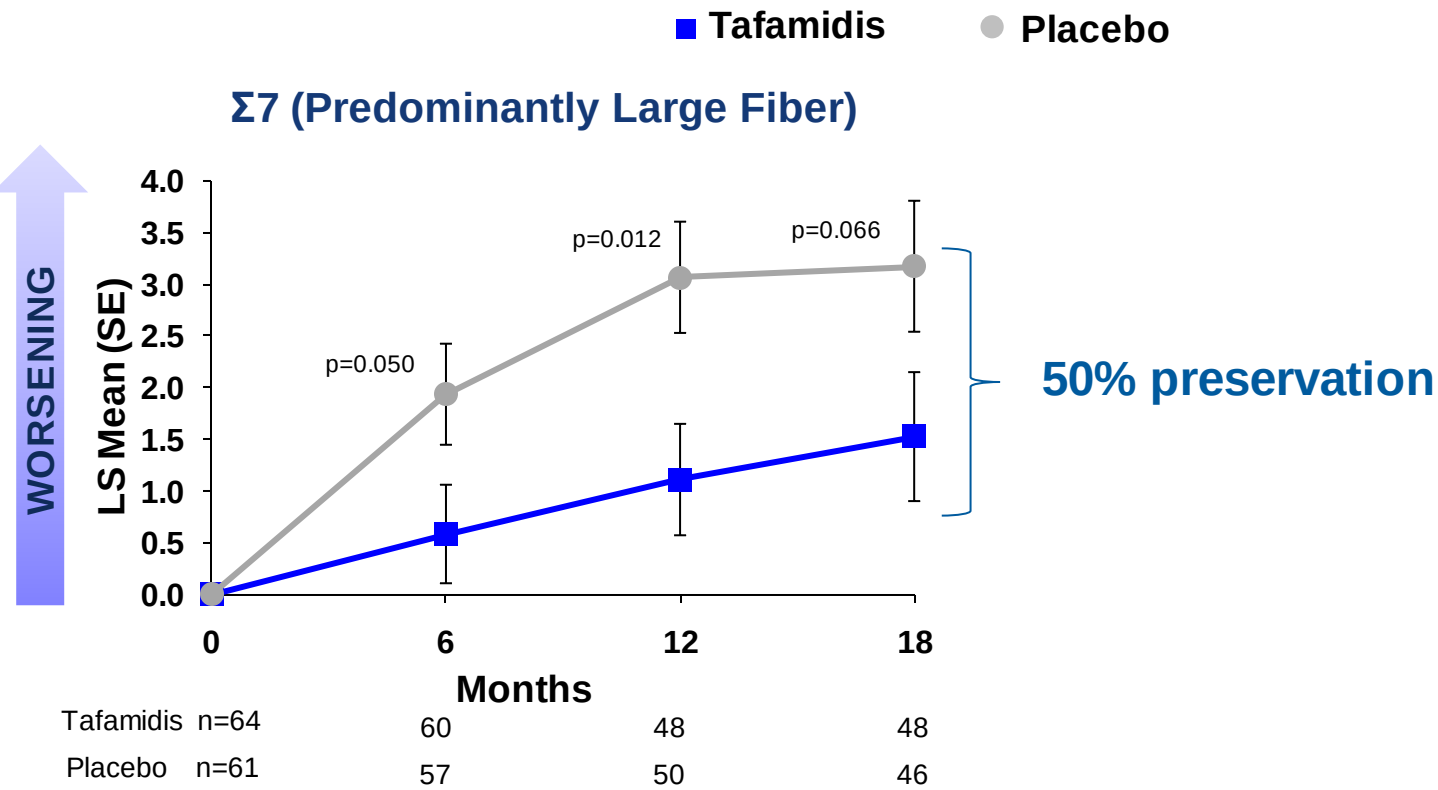


Σ7 Score – Change from Baseline to Month 18 by Site

Fx-005

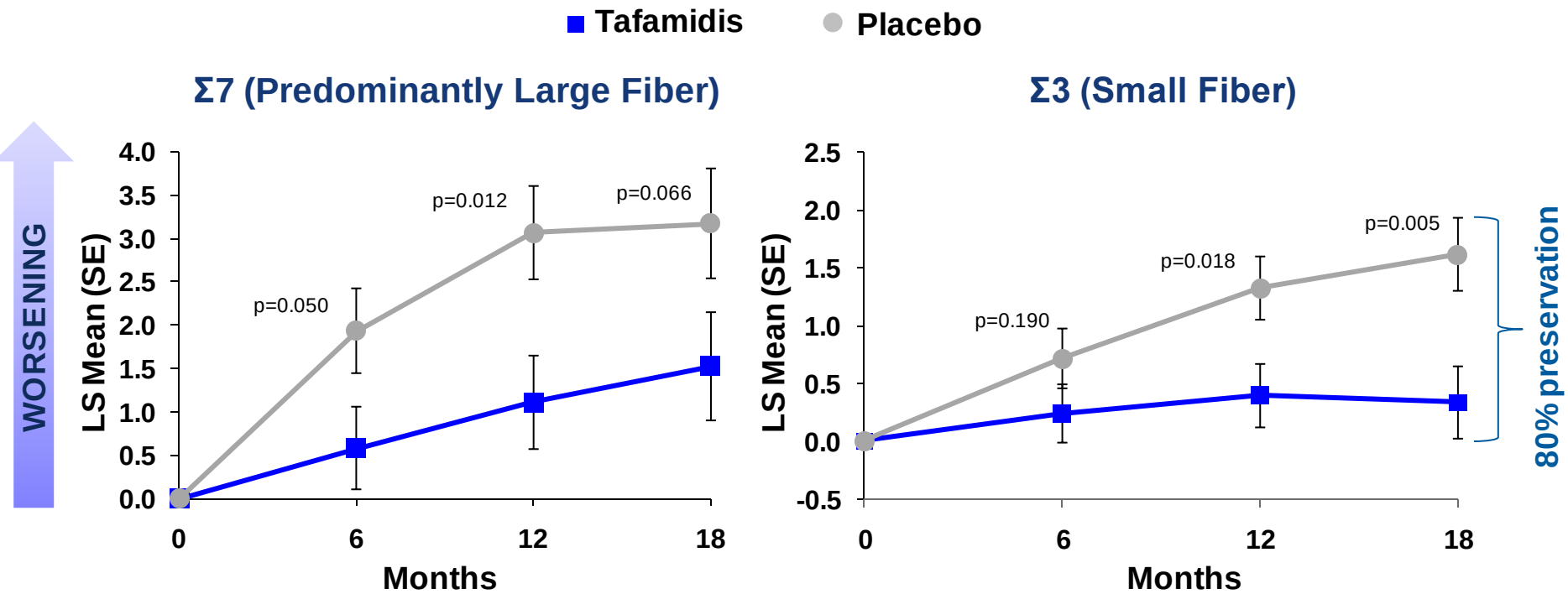


Neurophysiologic Measures
Change from Baseline to Months 6, 12 and 18 – Fx-005 (ITT)



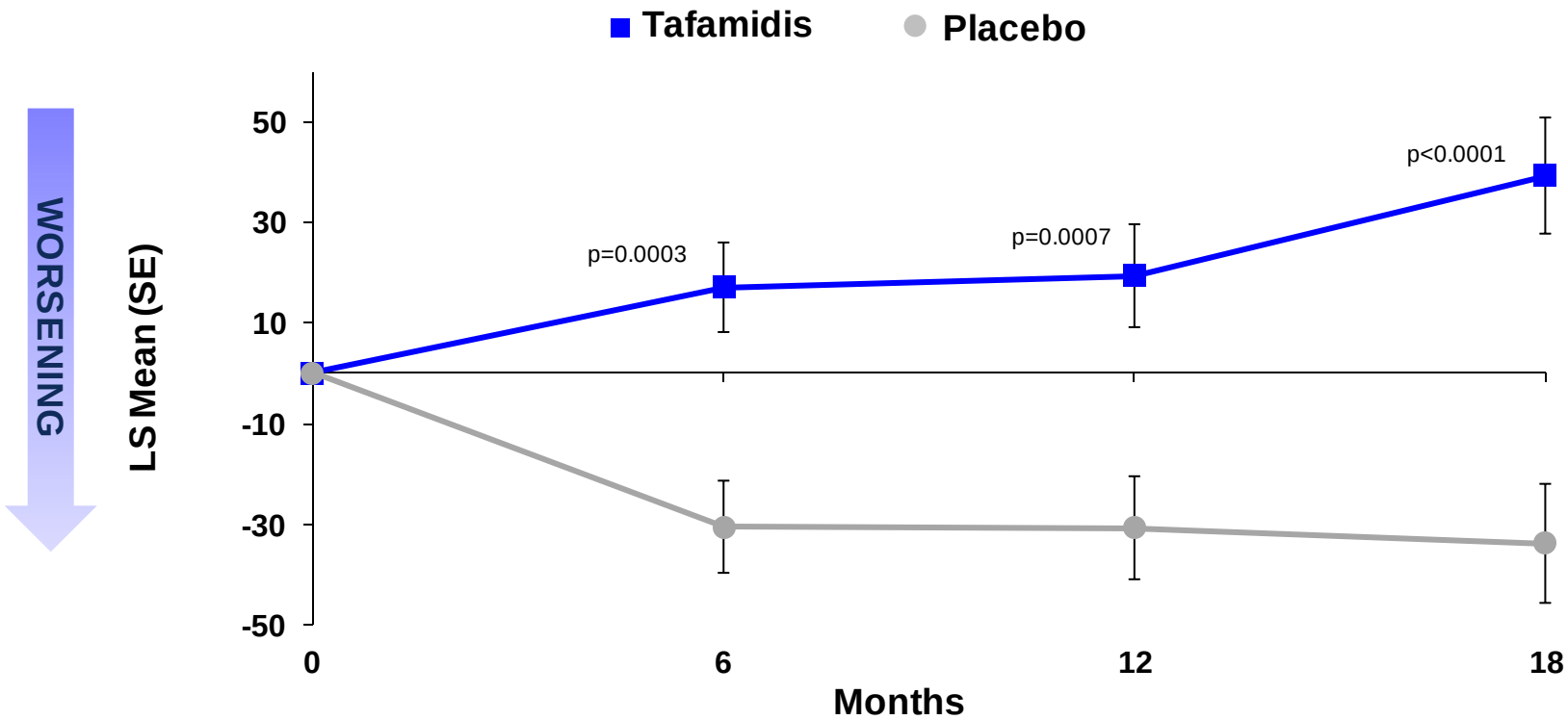
p-values based on repeated measures analysis of variance

Neurophysiologic Measures
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

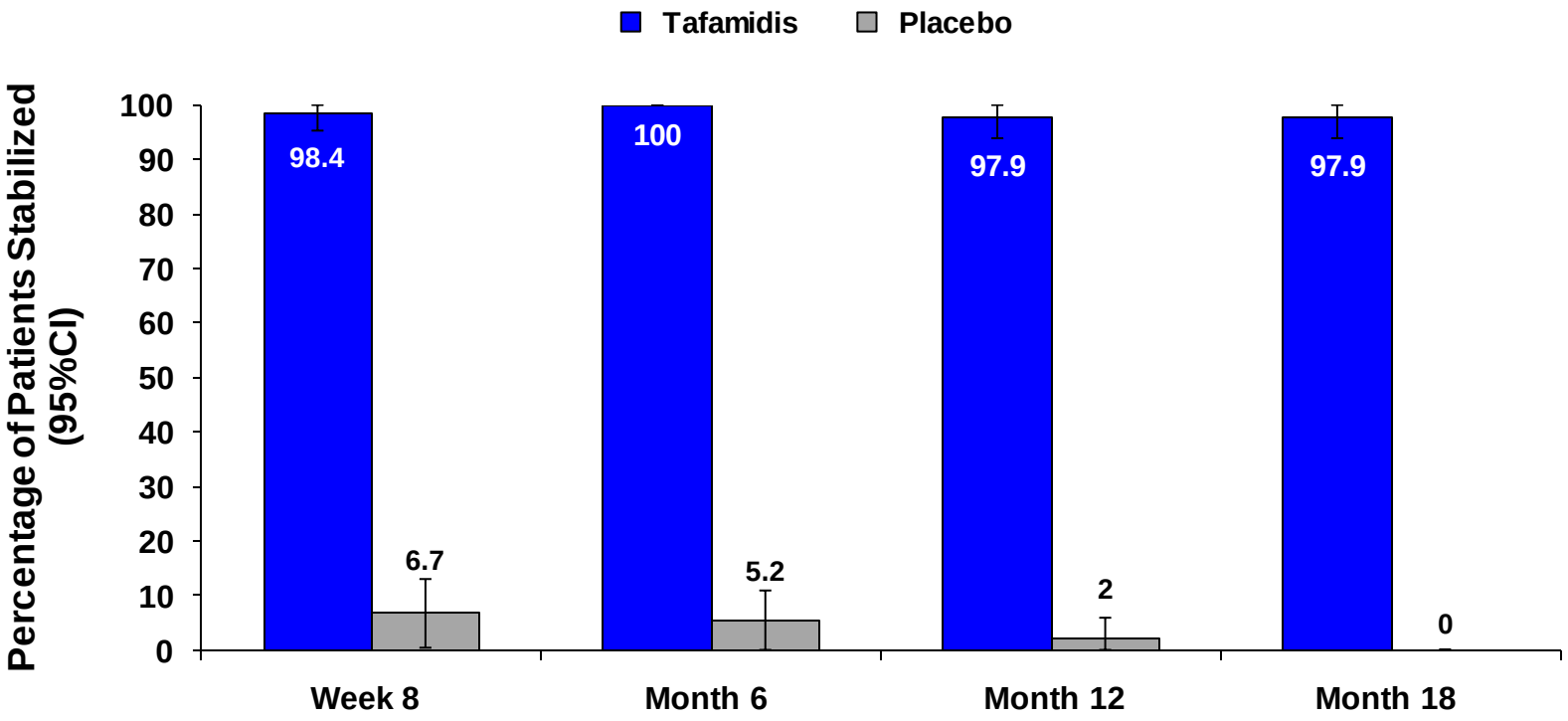
mBMI - Change from Baseline- Mixed Model Repeated Measures Fx-005 (ITT, OC)



Tafamidis N= 64	60	49	49
Placebo N= 61	56	50	46

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

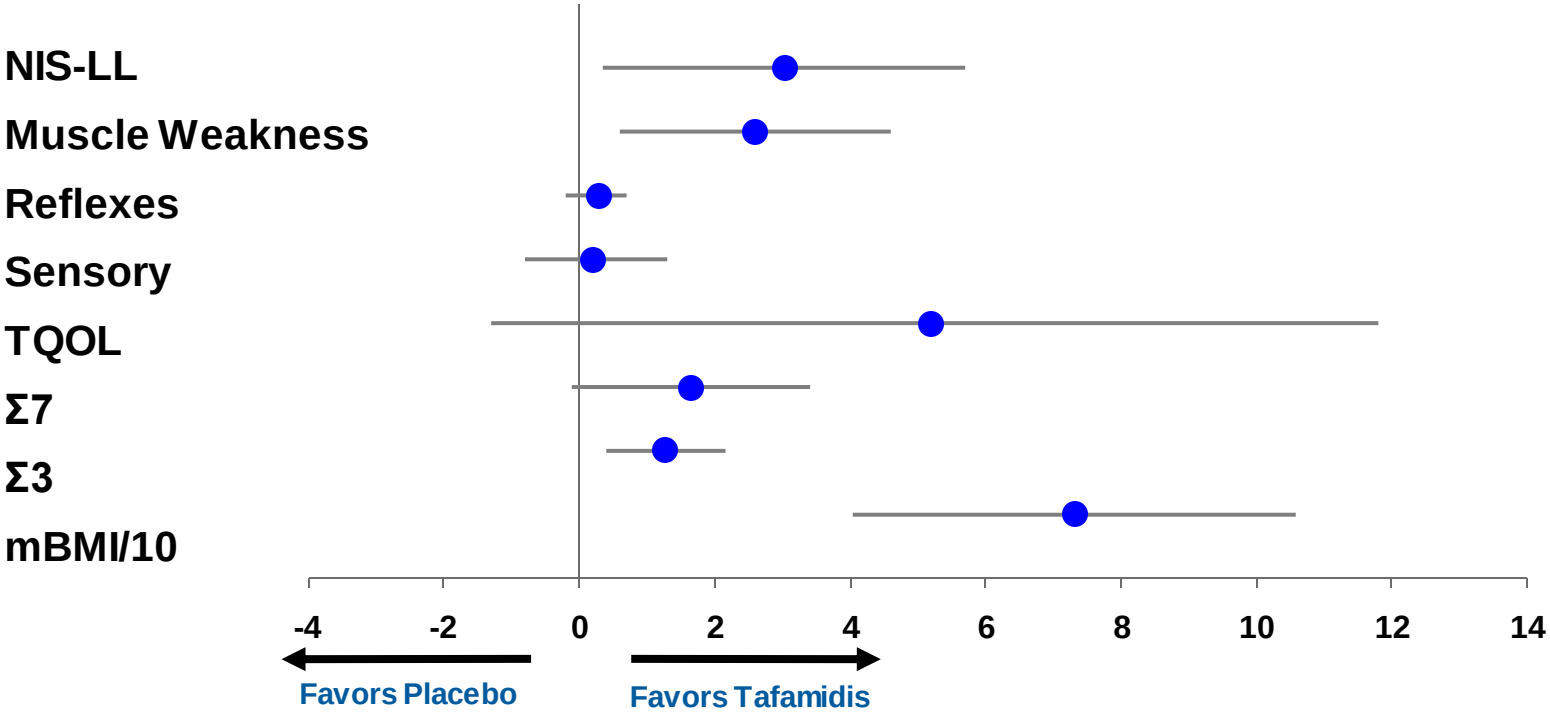
TTR Stabilization
Fx-005 (ITT)



	Week 8	Month 6	Month 12	Month 18
Tafamidis N=64	63	59	48	48
Placebo N=61	60	58	50	44

Consistent Results Across Efficacy Endpoints

Fx-005 (ITT)



Mean Change from Baseline at Month 18 (95%CI)

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

Tafamidis Polyneuropathy Development Program

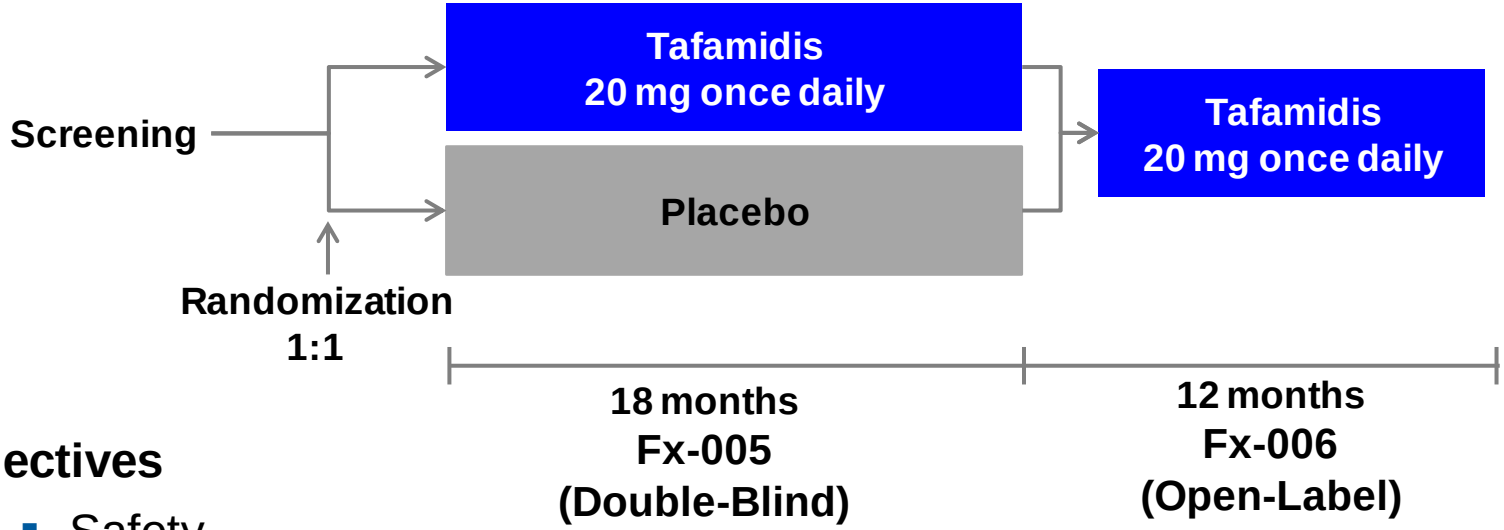
Study Fx-005	
18-month, randomized double-blind, placebo-controlled study	Pivotal study in V30M patients with TTR-FAP

Study Fx1A-201	
Open-label, multicenter, 12-month study	Transthyretin stabilization in patients with non-V30M mutations

Study Fx-006	
12-month, open-label extension for Fx-005	Long-term safety and efficacy

Study Fx1A-303	
Open-label, multicenter, 36-month study	Long-term extension study for Fx-006 and Fx1A-201 (study is ongoing)

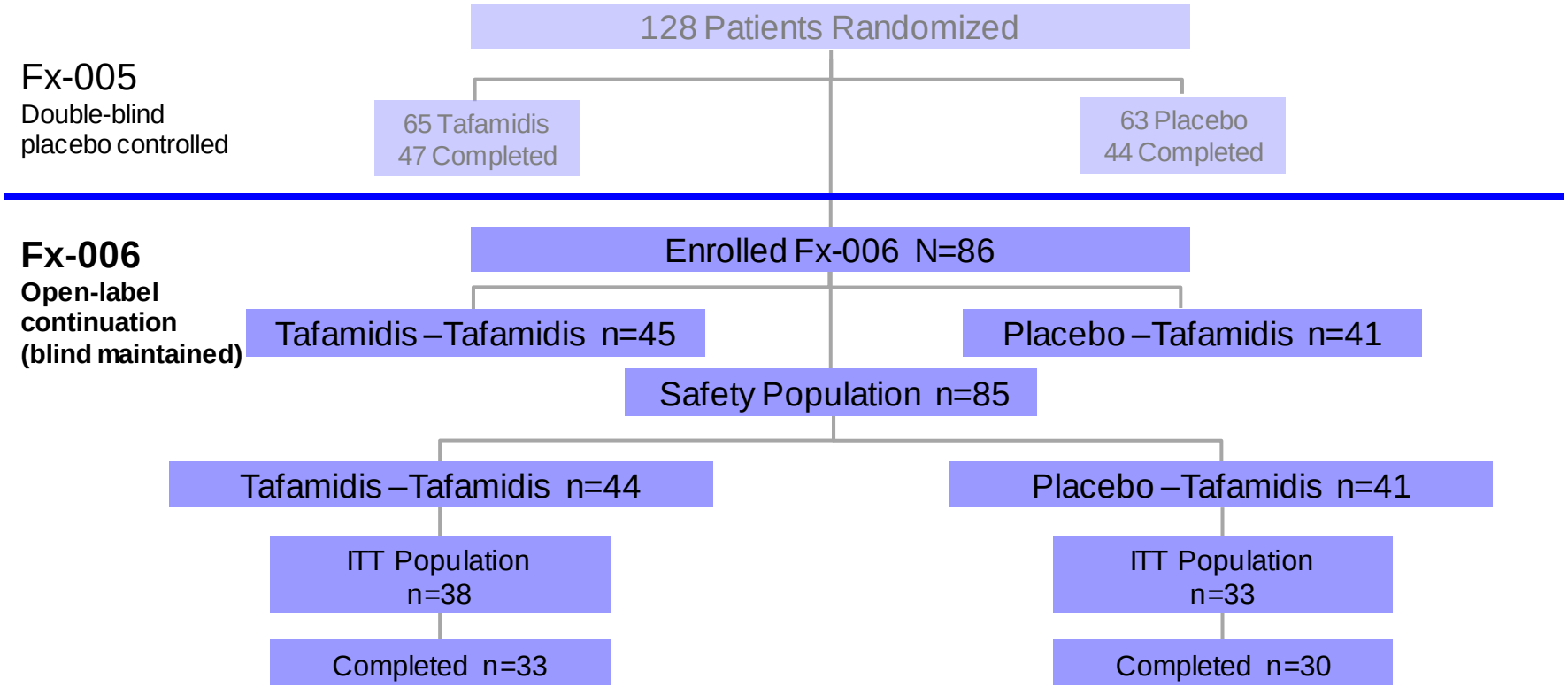
Overview of Pivotal Study (Fx-005) and Extension (Fx-006) Study Design and Objectives



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



Baseline Demographics
Fx-006 (ITT)

		Tafamidis-Tafamidis N=38	Placebo-Tafamidis N=33	p-value*
Age, years	Mean (SD) Median (Range)	42.0 (14.1) 37.5 (26, 76)	40.7 (13.7) 36.0 (24, 73)	0.537
Female	n (%)	21 (55.3)	18 (54.5)	1.000
Symptom duration, months	Mean (SD) Median (Range)	61.6 (55.4) 35.6 (21, 287)	53.7 (37.0) 36.8 (20, 152)	0.917

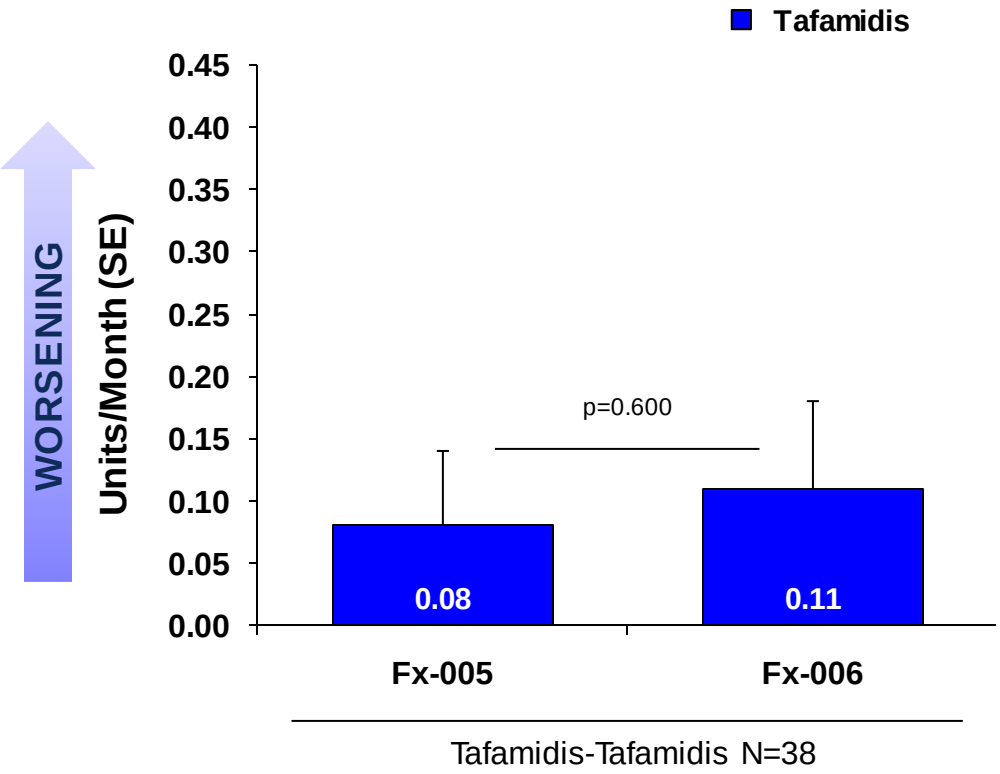
*p-values are based on Wilcoxon's Rank Sum test for continuous variables and Fisher's Exact Test for categorical variables

Baseline Disease Characteristics
Fx-006 (ITT)

		Tafamidis-Tafamidis N=38	Placebo-Tafamidis N=33	p-value*
NIS-LL	Mean (SD) Median (Range)	8.4 (13.2) 5.3 (0, 65)	17.5 (20.8) 10.0 (0, 75)	0.015
TQOL	Mean (SD) Median (Range)	21.1 (21.9) 11.0 (-1, 97)	38.1 (31.9) 28.0 (-1, 96)	0.020
Σ7	Mean (SD) Median (Range)	6.7 (8.5) 5.0 (-6.6, 25.3)	10.1 (10.7) 10.8 (-7.3, 25.1)	0.185
Σ3	Mean (SD) Median (Range)	4.8 (4.3) 4.2 (-2.5, 11.2)	7.1 (4.4) 7.4 (-2.1, 11.2)	0.020
mBMI	Mean (SD) Median (Range)	1068.4 (142.4) 1038.1 (780.1, 1473.7)	990.1 (265.0) 945.7 (567.5, 1583.8)	0.080

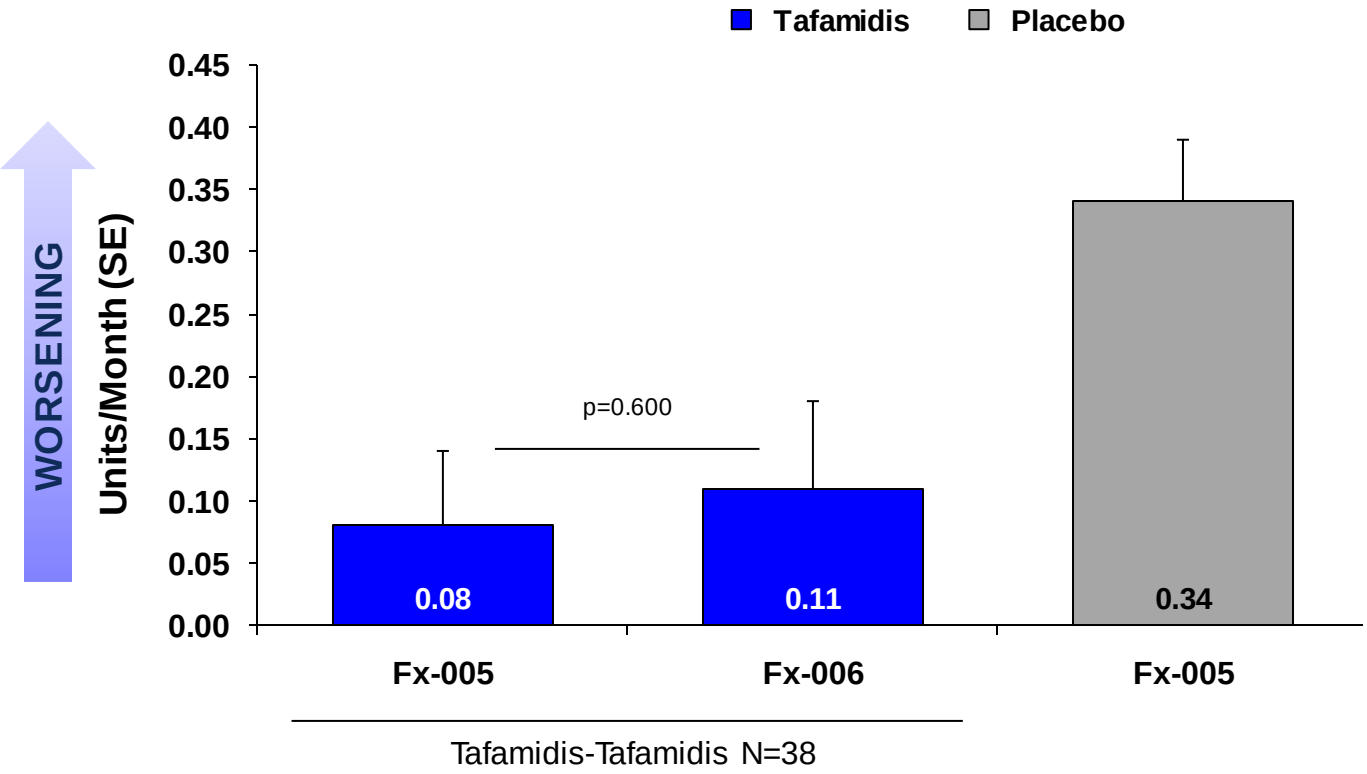
* p-values based on Wilcoxon Rank Sum Test

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

NIS-LL Monthly Rate of Change
Fx-006 (ITT)



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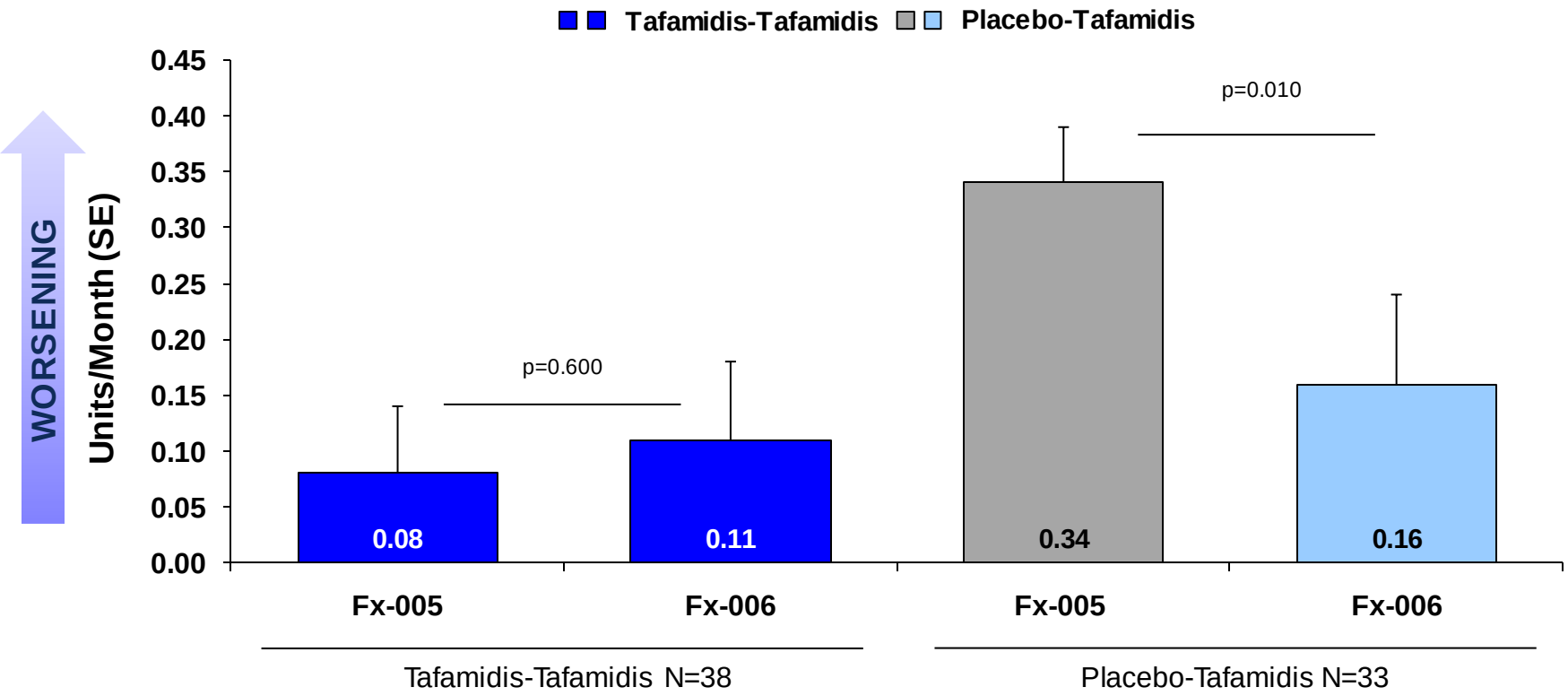
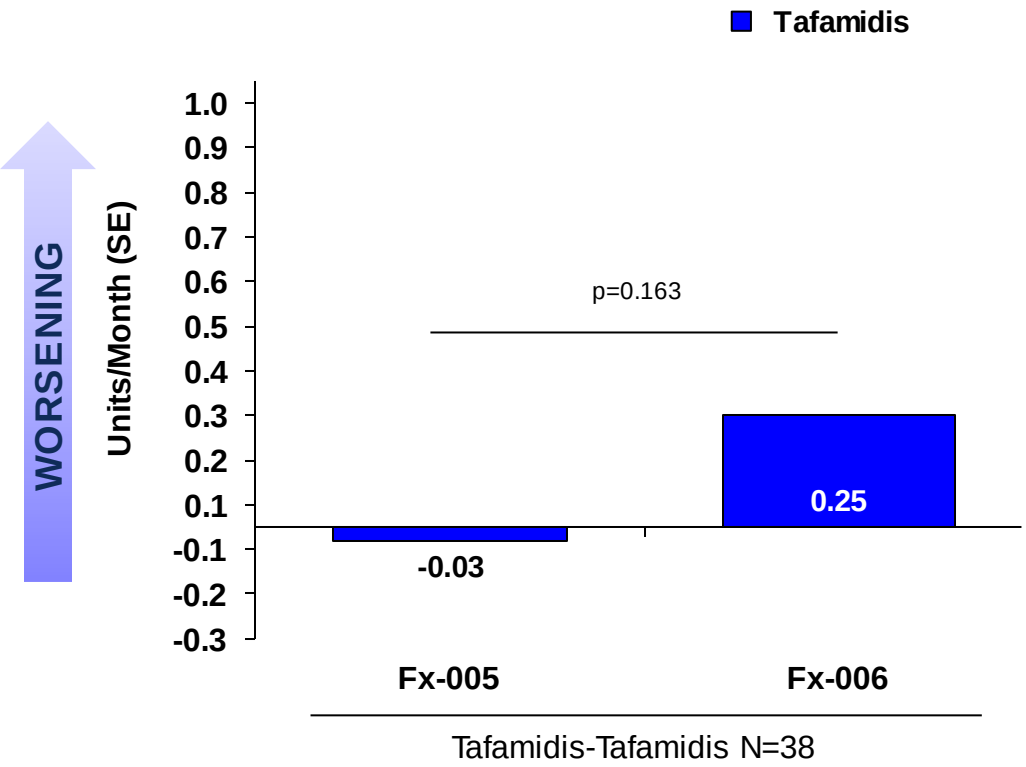


p-values comparing the rates of change based on a linear mixed model with the actual measurement as a dependent variable, study-by-treatment interaction and the time-by-study-by-treatment interaction as independent variables. The intercept and time variables were modeled as random effects.

TQOL Rate of Change
Fx-006 (ITT)



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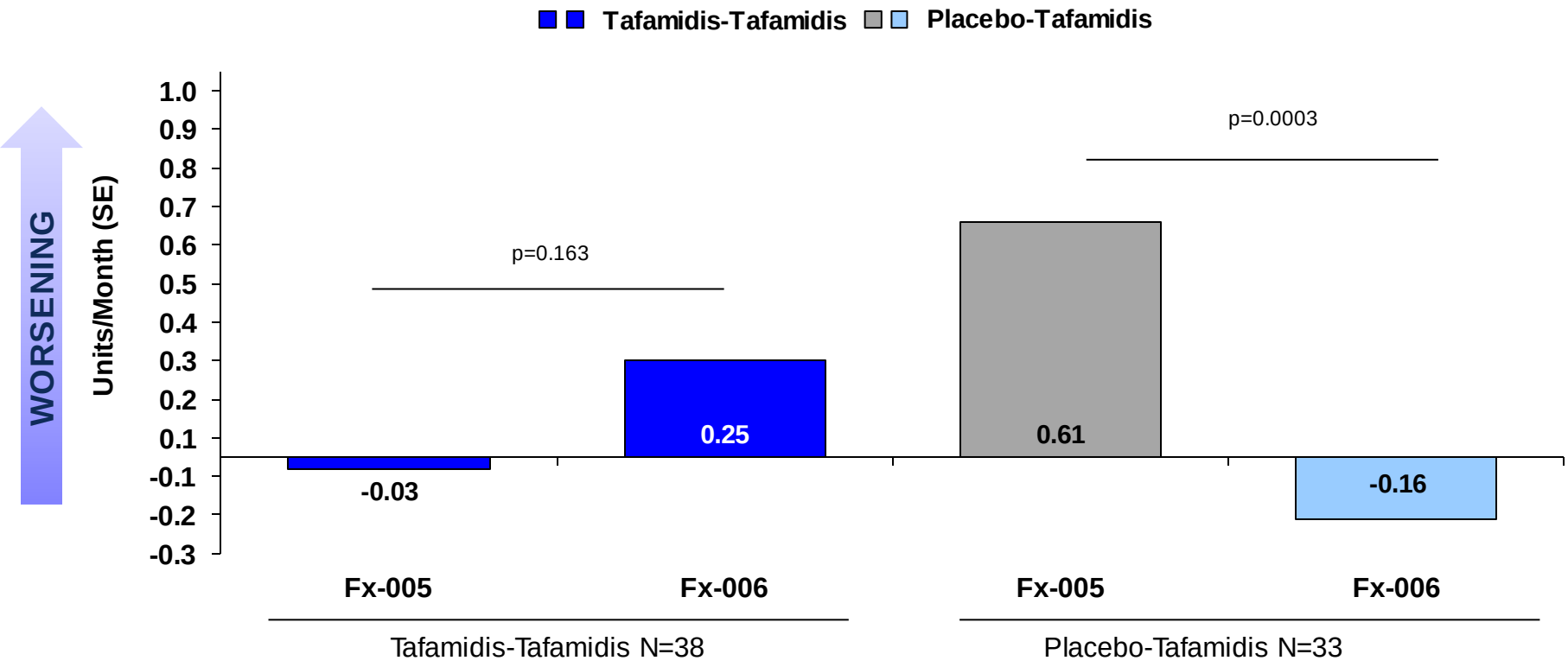
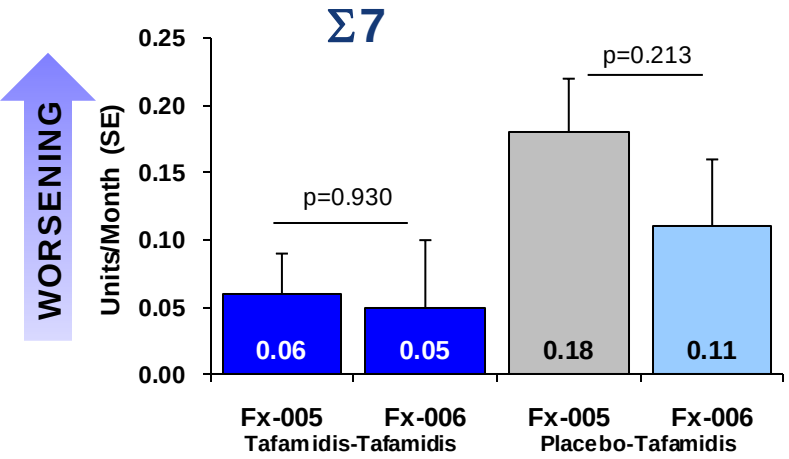
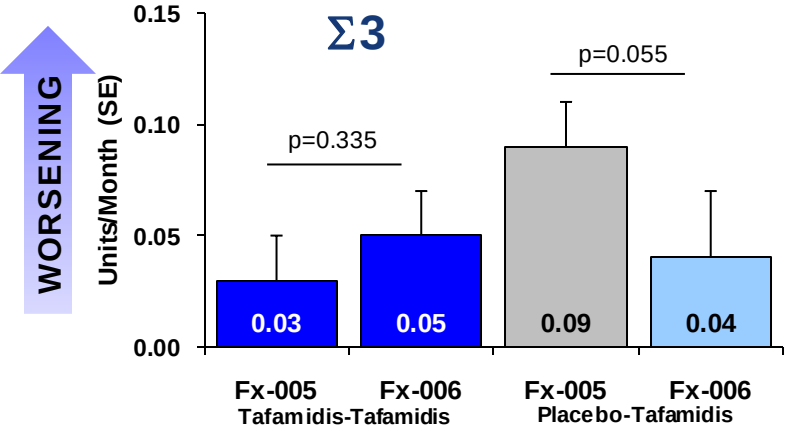
TQOL Rate of Change
Fx-006 (ITT)

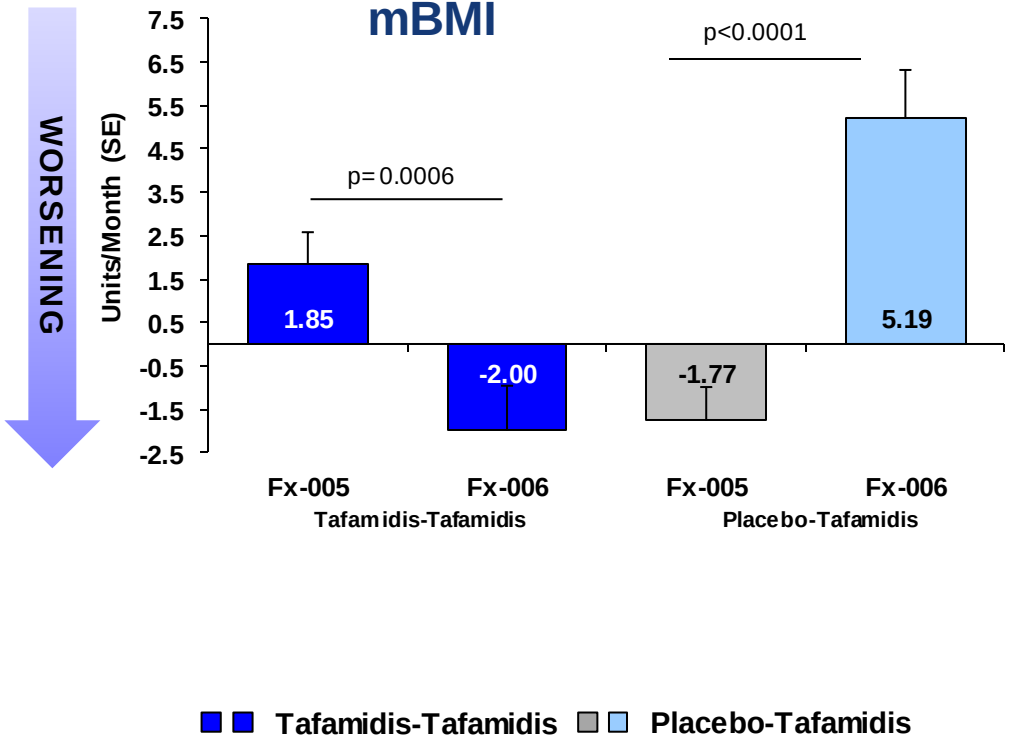


p-values comparing the rates of change based on a linear mixed model with the actual measurement as a dependent variable, study-by-treatment interaction and the time-by-study-by-treatment interaction as independent variables. The intercept and time variables were modeled as random effects.

Neurophysiological Measures and mBMI
Fx-006 (ITT)

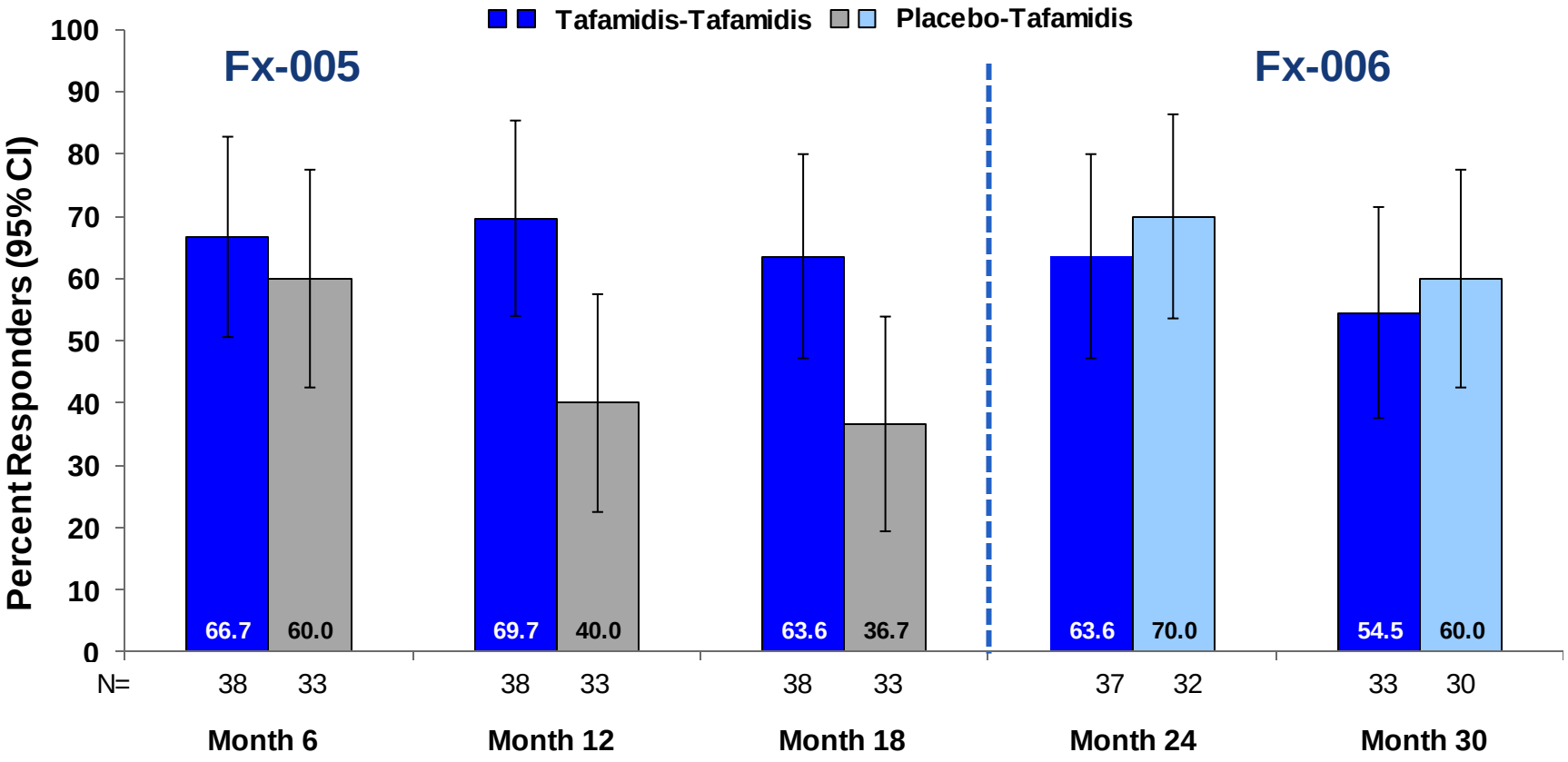






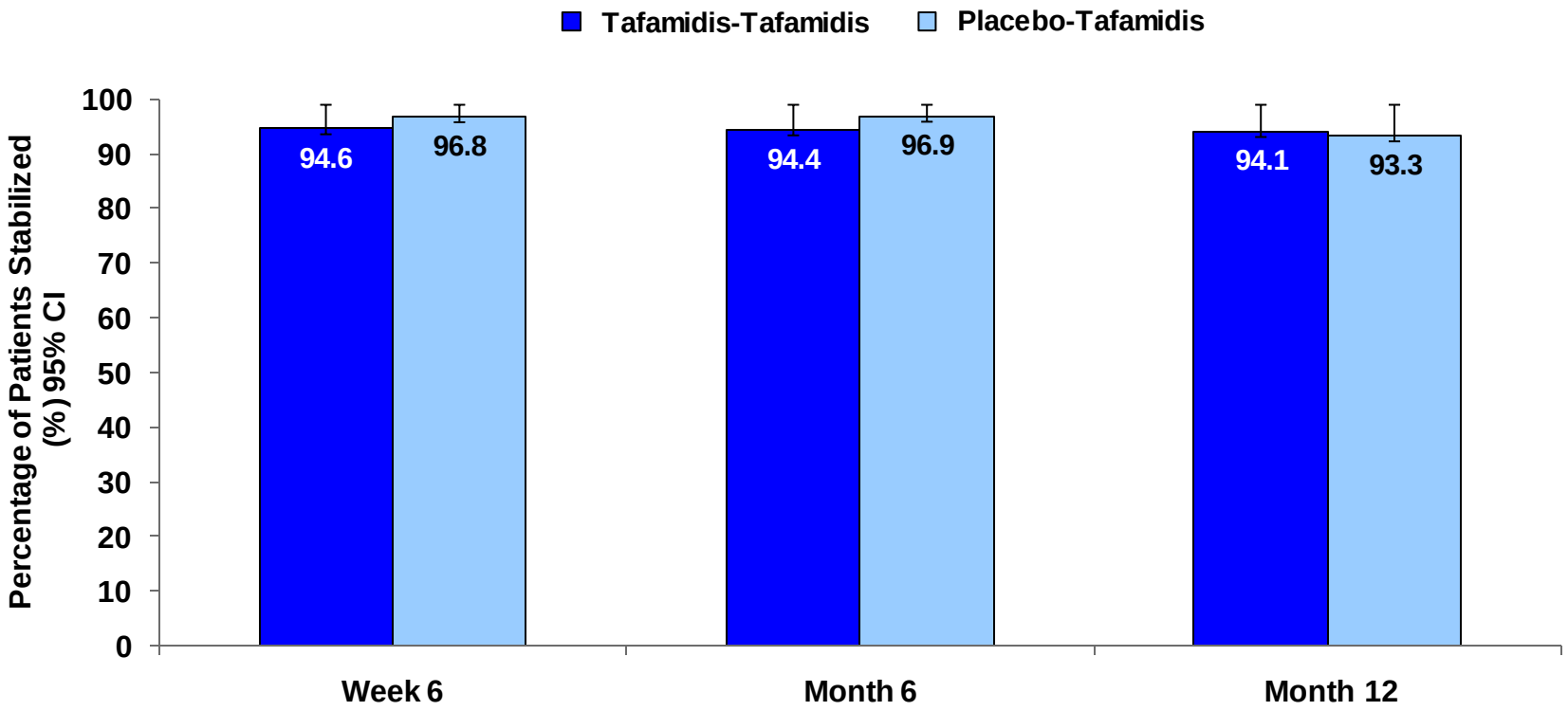
NIS-LL Responder Status to Month 30

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



	Week 6	Month 6	Month 12
Tafamidis	N=37	36	34
Placebo	N=31	32	30

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

Study Fx-005	
18-month, randomized double-blind, placebo-controlled study	Pivotal study in V30M patients with TTR-FAP

Study Fx1A-201	
Open-label, multicenter, 12-month study	Transthyretin stabilization in patients with non-V30M mutations

Study Fx-006	
12-month, open-label extension for Fx-005	Long-term safety and efficacy

Study Fx1A-303	
Open-label, multicenter, 36-month study	Long-term extension study for Fx-006 and Fx1A-201 (study is ongoing)

Study Fx1A-201

- Open label, 12-month study in patients with TTR-FAP who have a mutation other than V30M

Primary Endpoint	**TTR stabilization at 6 weeks**
Secondary Endpoints	**NIS (including NIS-LL), TQOL, Σ5 (NCS), HRDB, mBMI**

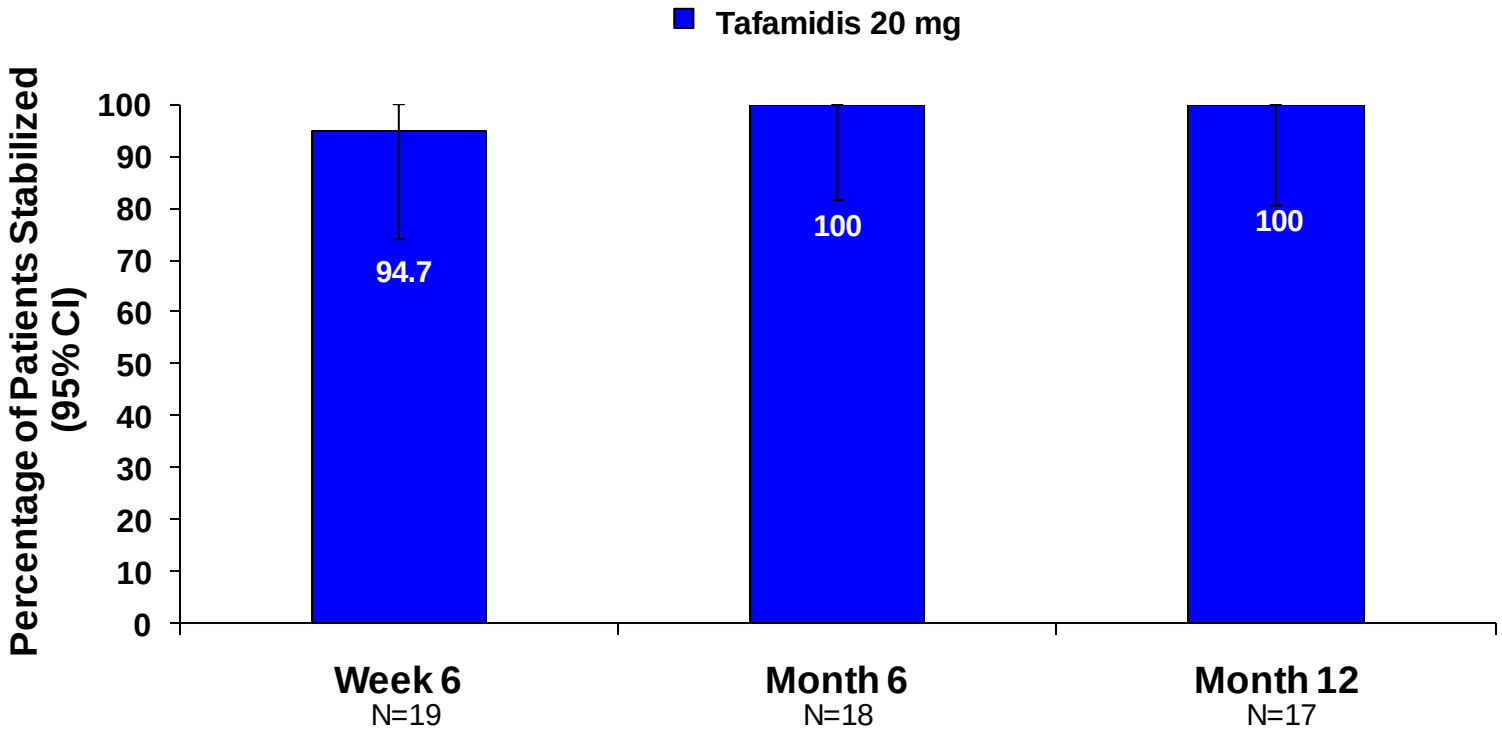
- 21 patients with 8 different mutations enrolled (N)
  - Leu58His (4)* Gly47Ala (3)*
  - Ser77Tyr (2)* Ser77Phe (1)
  - Ile107Val (2) Thr60Ala (4)*
  - Phe64Leu (4)* Asp38Ala (1)*

* TTR mutations reported from US in FAPWTR or enrolled from US site

Baseline Demographics and Disease Characteristics
Fx1A-201 (ITT)

		Fx-1A-201 Tafamidis N=21
Age (years)	Mean (SD) Median (Range)	63.1 (9.9) 64.3 (43.9, 76.8)
Female	n (%)	8 (38.1)
mBMI	Mean (SD) Median (Range)	1052.5 (206.7) 1047.8 (725.0, 1409.6)
Disease Duration (months)	Mean (SD) Median (Range)	64.7 (60.8) 45.5 (5.2, 253.1)
NIS-LL	Mean (SD) Median (Range)	27.6 (24.7) 18.0 (0.0, 69.9)
TQOL	Mean (SD) Median (Range)	47.8 (35.1) 38.0 (5.0, 104.0)
Σ5	Mean (SD) Median (Range)	6.1 (5.9) 6.7 (-3.7, 14.8)

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.

Secondary Endpoints - Change from Baseline to Month 12
Fx1A-201

	Fx1A-201 Mean (SD)	Fx-005 Mean (SD)	
NIS-LL	Tafamidis N=18	Tafamidis N=49	Placebo N=50
Month 12	2.70 (6.27)	1.35 (0.80)	4.72 (0.80)
mBMI			
Month 12	16.6 (89.33)	19.4 (10.23)	-30.7 (10.24)
Σ5 (NCS)			
Month 12	0.20 (0.20)	0.70 (3.43)	2.30 (3.17)
TQOL			
Month 12	-1.40 (11.71)	1.50 (2.31)	4.5 (2.31)

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

Endpoint	Benefit of Tafamidis Measured by Endpoint
• **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

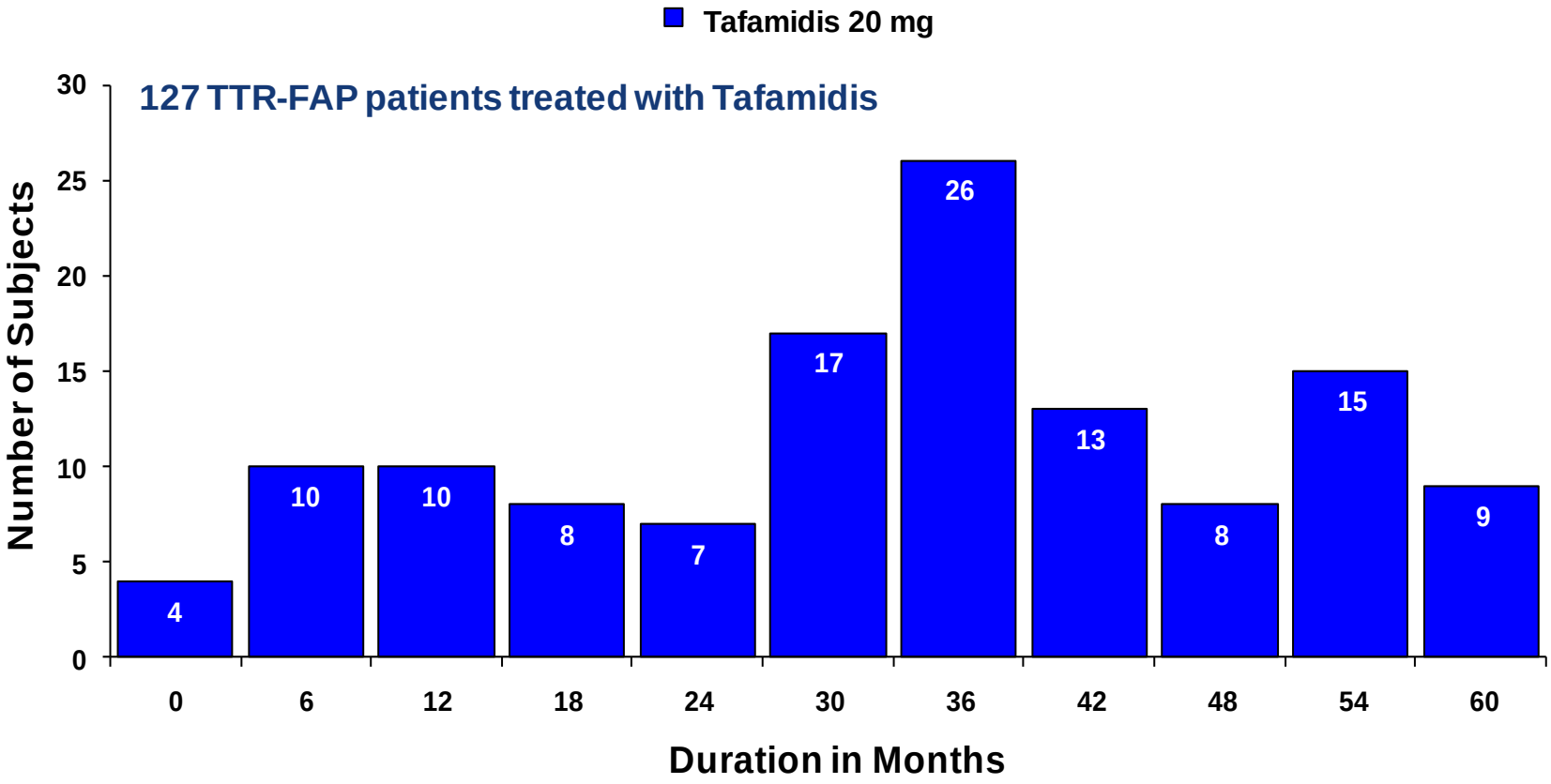
Additional Confirmatory Evidence of Efficacy
Fx-006, Fx1A-201

- 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)



Discontinuations Due to Adverse Events
Fx-005

Discontinuations		
Primary Reason, n (%)	Tafamidis N=65	Placebo N=63
Adverse Event	4 (6.2)	3 (4.8)
Patient Withdrew Consent	1 (1.5)	2 (3.2)
Liver Transplant	13 (20.0)	13 (20.6)
Patient Died	0	0
Other	0	1 (1.6)

Discontinuations Due to AEs		
	Adverse Event	Onset Day
Tafamidis	Diarrhea	Day 133
	Nausea	Day 16
	Urticaria*	Day 190
	Pregnancy	Day 169
Placebo	Fatigue, Paresthesia	Day 167
	Nausea, Unintentional weight loss	Day 38
	Worsening Cardiac amyloidosis*	Day 409

* Serious adverse event

Most Common AEs (≥10%)

Fx-005

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

= Tafamidis > Placebo

Serious Adverse Events (SAEs)
Fx-005

Tafamidis 6 patients (9.2%) with SAEs	Placebo 5 patients (7.9%) with SAEs
Viral Infection	Pneumothorax Cardiac Amyloidosis
Conduction disorder	Syncope, Anemia Peripheral edema
Urticaria	Staphylococcal infection – pacemaker site; Lymphangitis, Cellulitis – right leg; Cellulitis – left foot; Skin Ulcer – left foot
Urinary Tract Infection	Hypertensive emergency; Third degree burns
Localized Infection – foot	Nausea; Vomiting; Catheter site phlebitis
Pneumonia, UTI	

Deaths
Fx-005

Deaths in Fx-005 (all occurred post-liver transplant)	
Tafamidis	**Placebo**
Cardiac tamponade (following pacer placement for liver transplantation)	Sepsis (approximately 6 months after liver transplantation)
Unknown cause (approx. 3 months after liver transplantation at a different hospital)	Hepatic Failure (following transplant, died despite re-transplantation)
	Unknown cause (10 days after liver transplant)

Summary Description of Patients with UTIs
Fx-005

	Tafamidis N=65 (%)	Placebo N=63 (%)
Number of patients with ≥1 UTI	17 (26.2)	9 (14.3)
Gender (Female : Male)	12:5	5:4
Number patients with Serious UTIs	2 (11.8)	0
Number of patients treated with antibiotics	16 (94.1)	9 (100.0)
Number of patients with mild or moderately severe UTI	16 (94.1)	8 (88.9)
Number of patients who discontinued study drug	0	0
Number of patients recovered/recovering	16 (94.1)	8 (88.9)

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

System Organ Class Preferred Term, n (%)	Tafamidis N=65	Placebo N=63
Gastrointestinal disorders		
Diarrhea	17 (26.2)	12 (19.0)
Upper abdominal pain	8 (12.3)	2 (3.2)
Infections and infestations		
Urinary tract infection†	17 (26.2)	9 (14.3)
Vaginal infection*	6 (9.2)	3 (4.8)

† Preferred term: UTI, Escherichia UTI and Cystitis
* Preferred term: Vaginal infection, Vaginal candidiasis, Candidiasis

Tafamidis
Pharmacovigilance & Risk Management Activities

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

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:**
  - Same pathogenesis
  - 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

Andersson 1976; Hattori 2003; THAOS; Planté 1998; Gertz 1992, Kim 2009, FAPWTR

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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

Endpoint	Benefits Measured by Endpoint
• **Co-Primaries** Neuropathy Impairment Score-LL (NIS-LL) & Norfolk Quality of Life Questionnaire	Clinical benefit

Endpoints for Replication of Efficacy

Endpoint	Benefits Measured by Endpoint
• **Co-Primaries** Neuropathy Impairment Score-LL (NIS-LL) & Norfolk Quality of Life Questionnaire	Clinical benefit
• **Neurologic Function** NIS-LL and subscales (motor, sensory, reflex)	Measures of disease progression – likely to predict clinical benefit
• **Neurophysiologic Function** **Σ3, Σ7**	Measures of disease progression – likely to predict clinical benefit
• **Modified BMI**	Measure of overall disease severity with prognostic value in TTR-FAP – likely to predict clinical benefit in this setting of TTR-FAP

Endpoints for Replication of Efficacy

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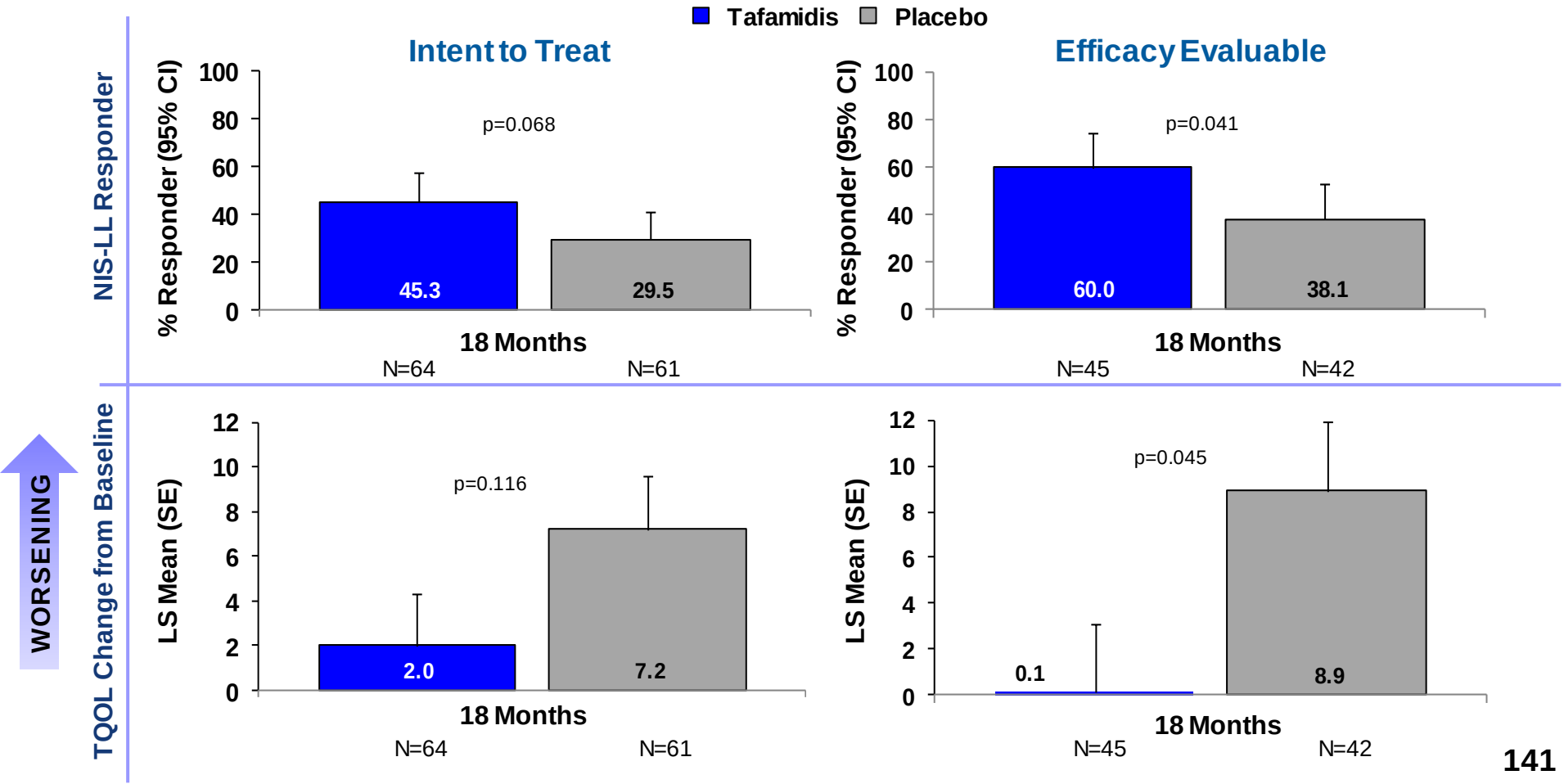
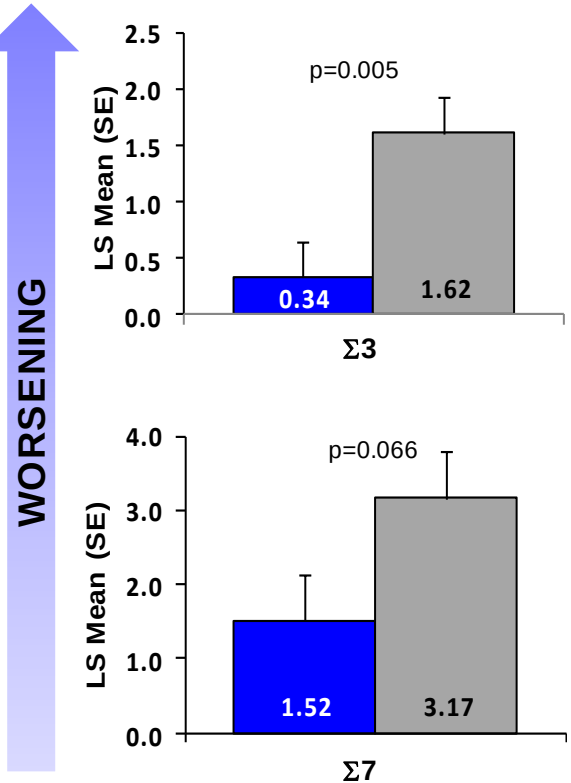
• **Modified BMI**	Measure of overall disease severity with prognostic value in TTR-FAP – likely to predict clinical benefit in this setting of TTR-FAP
• **TTR Stabilization**	Blocks rate-limiting step in disease – biologically plausible marker

Primary Endpoints: Evidence of Clinical Benefit

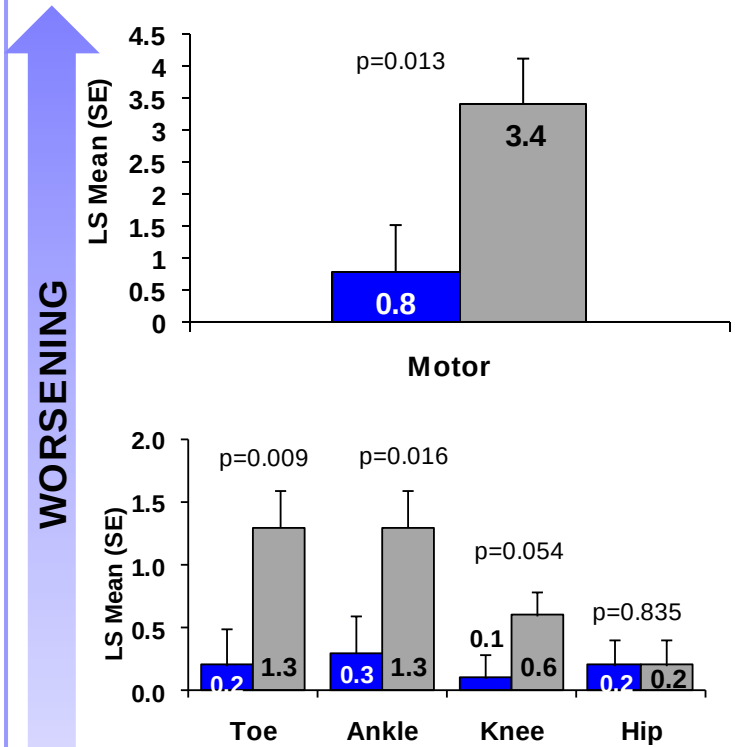


Consistent Effects Across Independent Efficacy Measures of Disease Progression at 18 Months – Fx-005

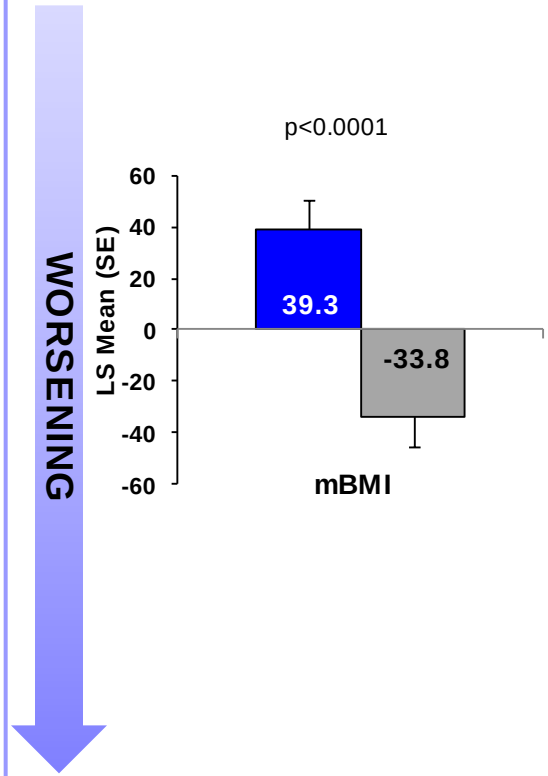
Neurophysiology



NIS-LL Muscle Strength



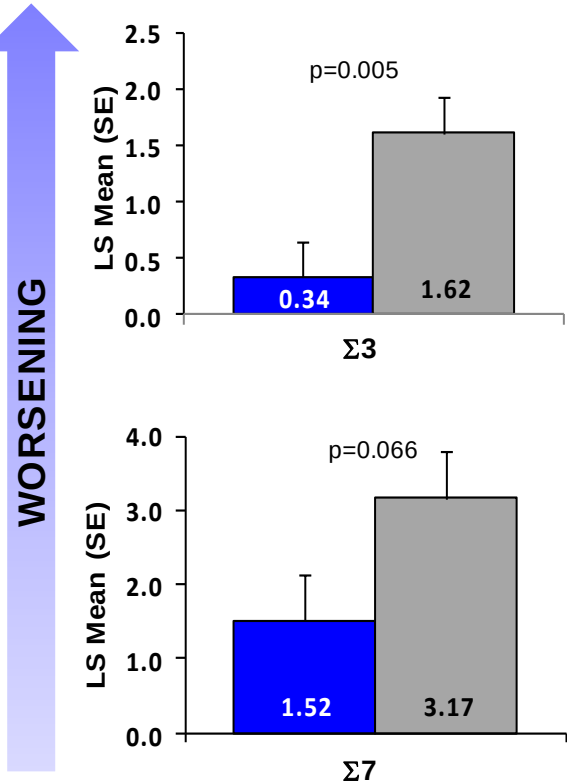
mBMI



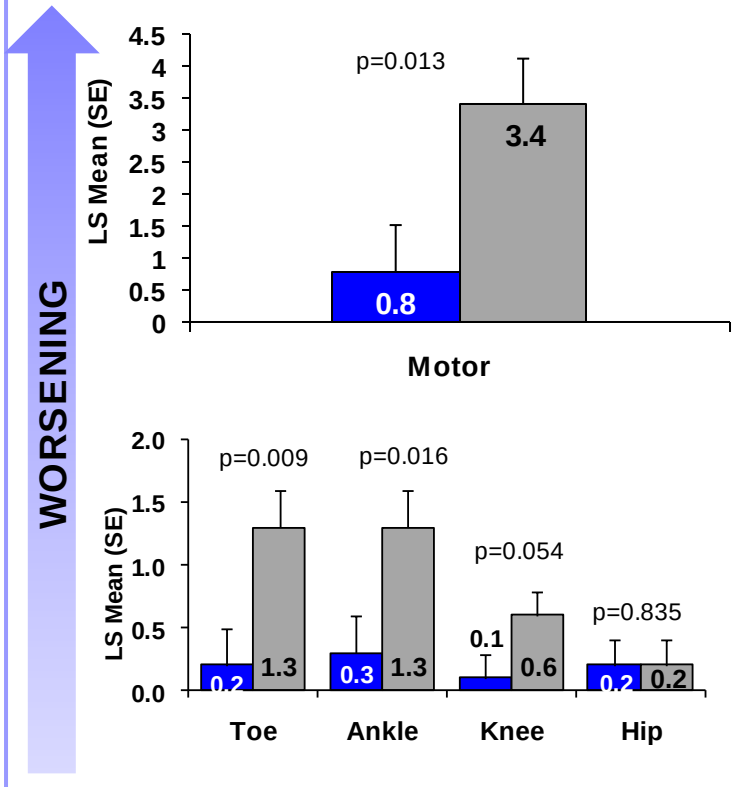
■ Tafamidis N=64 ☐ Placebo N=61

Consistent Effects Across Independent Efficacy Measures of Disease Progression at 18 Months – Fx-005

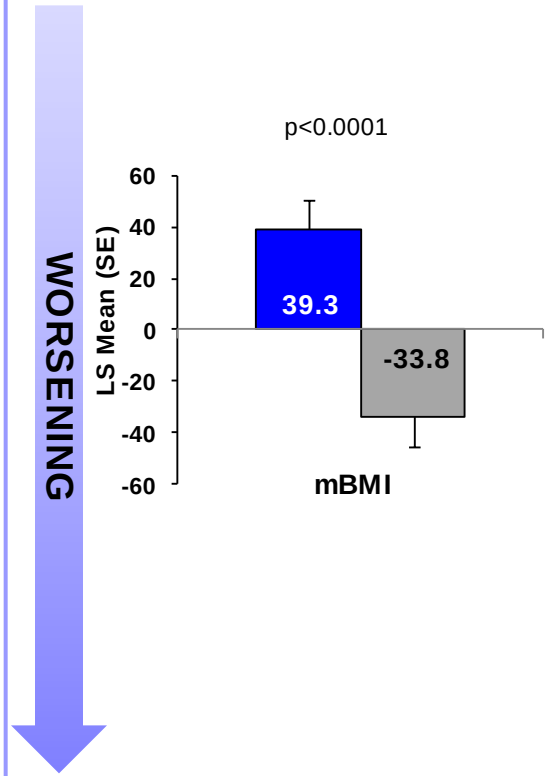
Neurophysiology



NIS-LL Muscle Strength



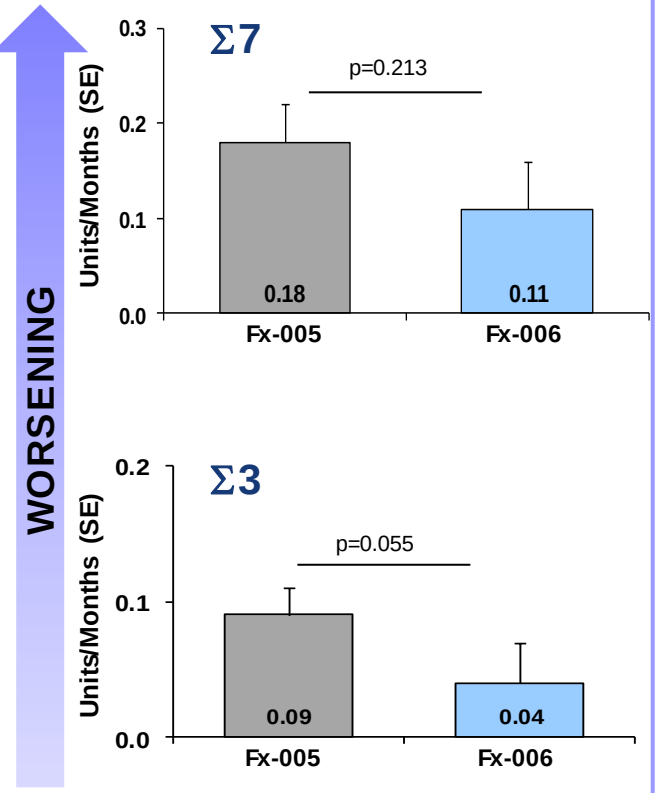
mBMI



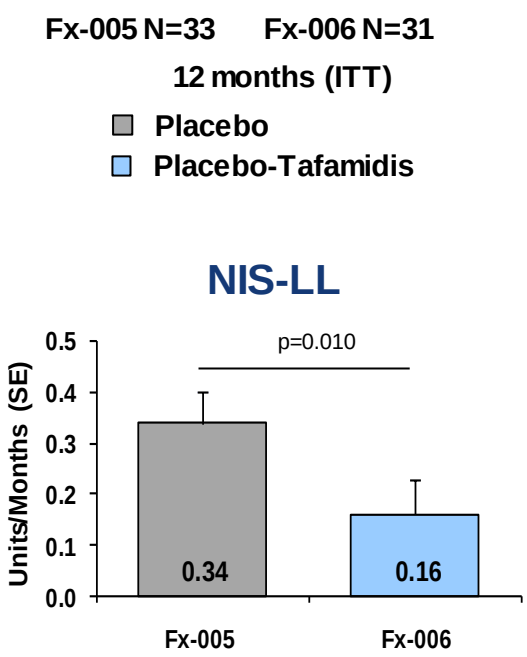
Tafamidis N=64 Placebo N=61

FX-006 Provides Confirmatory Support to FX-005

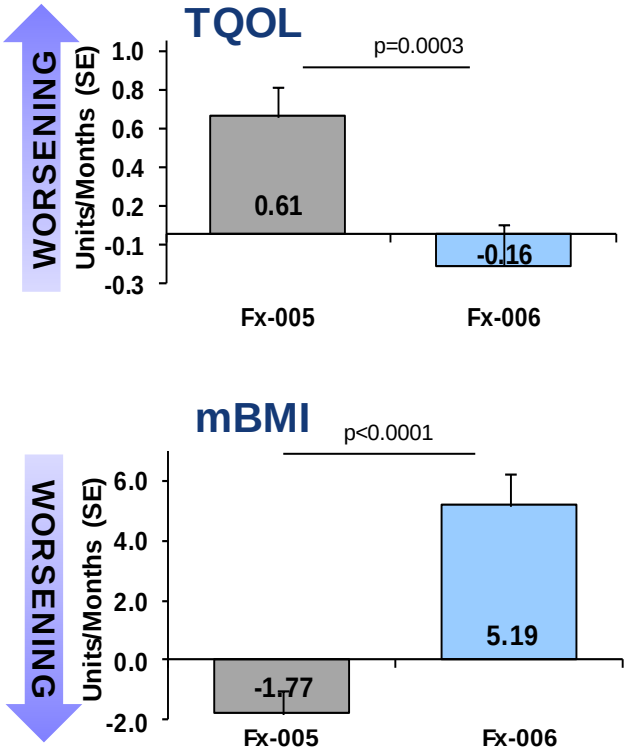
Neurophysiology



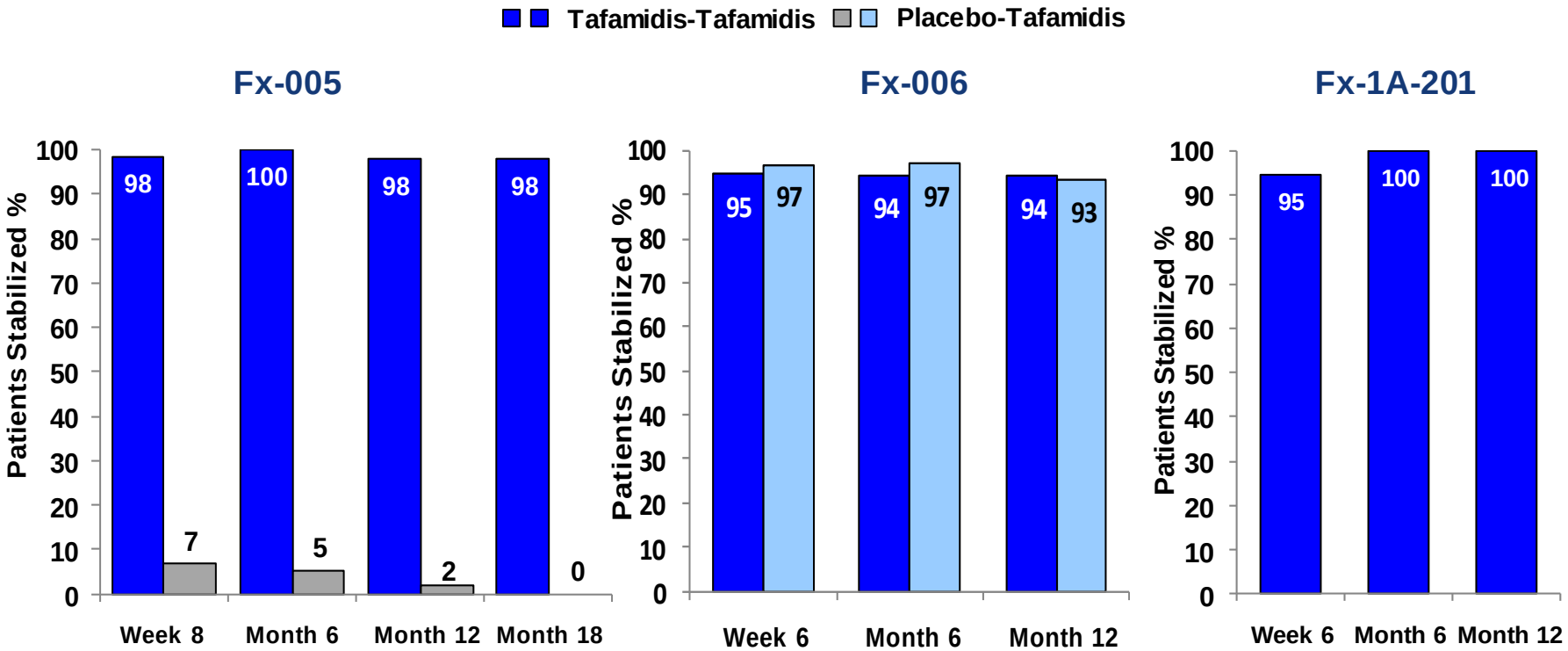
NIS-LL



TQOL/ mBMI



TTR Stabilization Across the Tafamidis Program



	Week 8	Month 6	Month 12	Month 18
Tafamidis	n= 63	59	48	48
Placebo	n= 60	58	50	44

	Week 6	Month 6	Month 12
Tafamidis	n= 37	36	34
Placebo	n= 31	32	30

	Week 6	Month 6	Month 12
Tafamidis	n= 19	n= 18	n= 17

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

Continued Clinical Data Collection

- 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

Subpart H is Most Suitable Means for Making Tafamidis Available to Patients

- 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

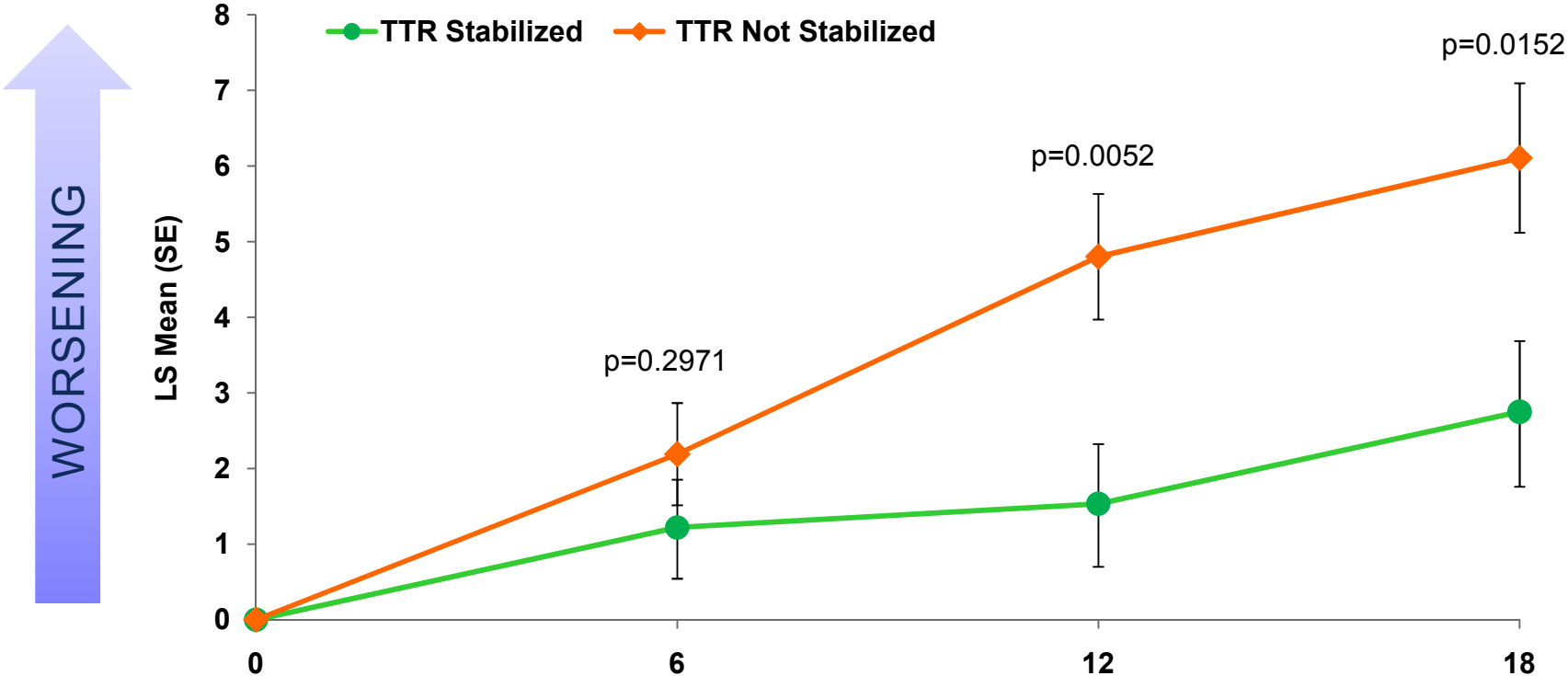
Positive Benefit:Risk Profile of Tafamidis Supports Approval

- 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

There is a Pressing Need for a Pharmacological Treatment for Patients with TTR-FAP

- 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

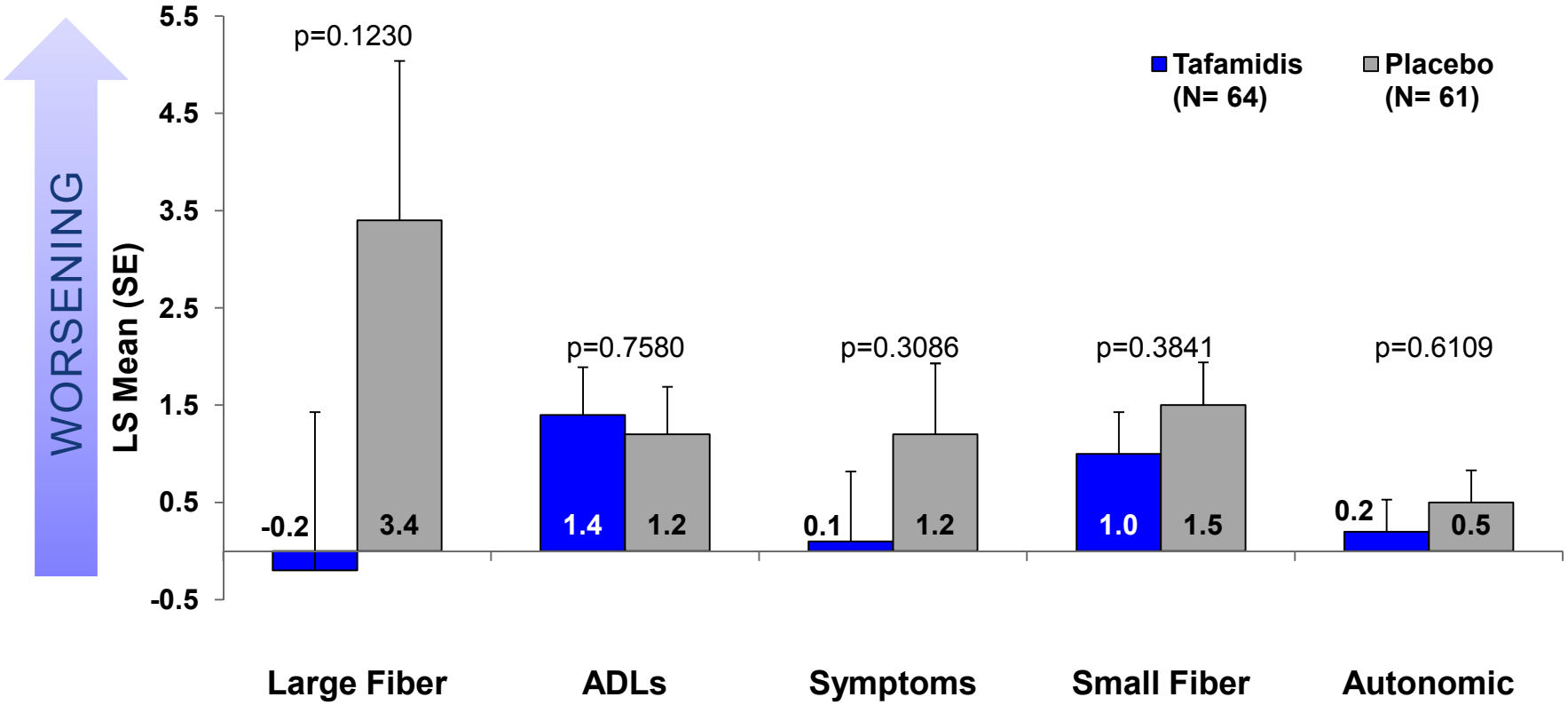
NIS-LL Change from Baseline by Week 8 TTR Stabilization Status at Months 6, 12, and 18 (ITT)



	0	6	12	18
Week 8 Stabilized N=66 (Tafamidis n=62, Placebo n=4)		62	51	50
Week 8 Not Stabilized N=57 (Tafamidis n=1, Placebo n=56)		54	47	44

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.

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



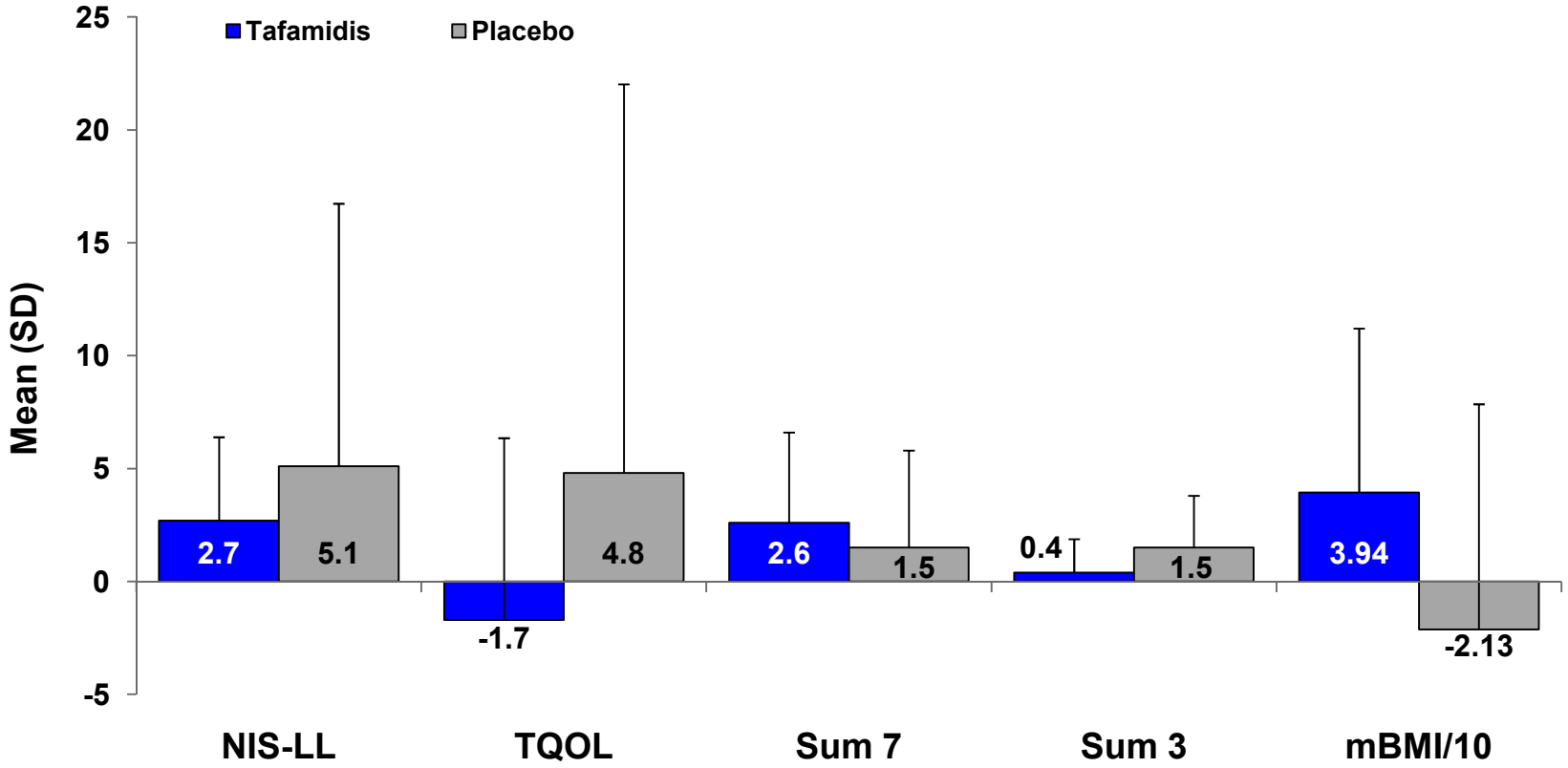
p-values based on repeated measures analysis of variance with change from baseline as the dependent variable, treatment, month and treatment-by-month as fixed effects and subject as a random effect in the model, and an unstructured covariance matrix

Fx-005 - Baseline Disease Characteristics For Subjects who had Liver Transplant (ITT)

		Liver Transplant	
		Tafamidis N=13	Placebo N=13
NIS-LL	Mean (SD)	15.1 (15.64)	13.8 (14.04)
	Median (Range)	10.0 (2.0, 53.5)	10.5 (2.0, 51.9)
TQOL	Mean (SD)	43.7 (20.38)	37.8 (21.18)
	Median (Range)	46.0 (12.0, 71.0)	33.0 (15.0, 86.0)
Σ 7	Mean (SD)	12.7 (8.38)	13.0 (5.66)
	Median (Range)	14.0 (-2.4, 24.3)	11.4 (4.9, 23.2)
Σ 3	Mean (SD)	8.1 (4.31)	7.1 (3.34)
	Median (Range)	11.2 (0.6, 11.2)	7.9 (2.4, 11.2)
mBMI	Mean (SD)	993.1 (181.49)	957.9 (165.62)
	Median (Range)	1028.7 (655.1, 1249.6)	958.2 (757.9, 1275.1)

Fx-005

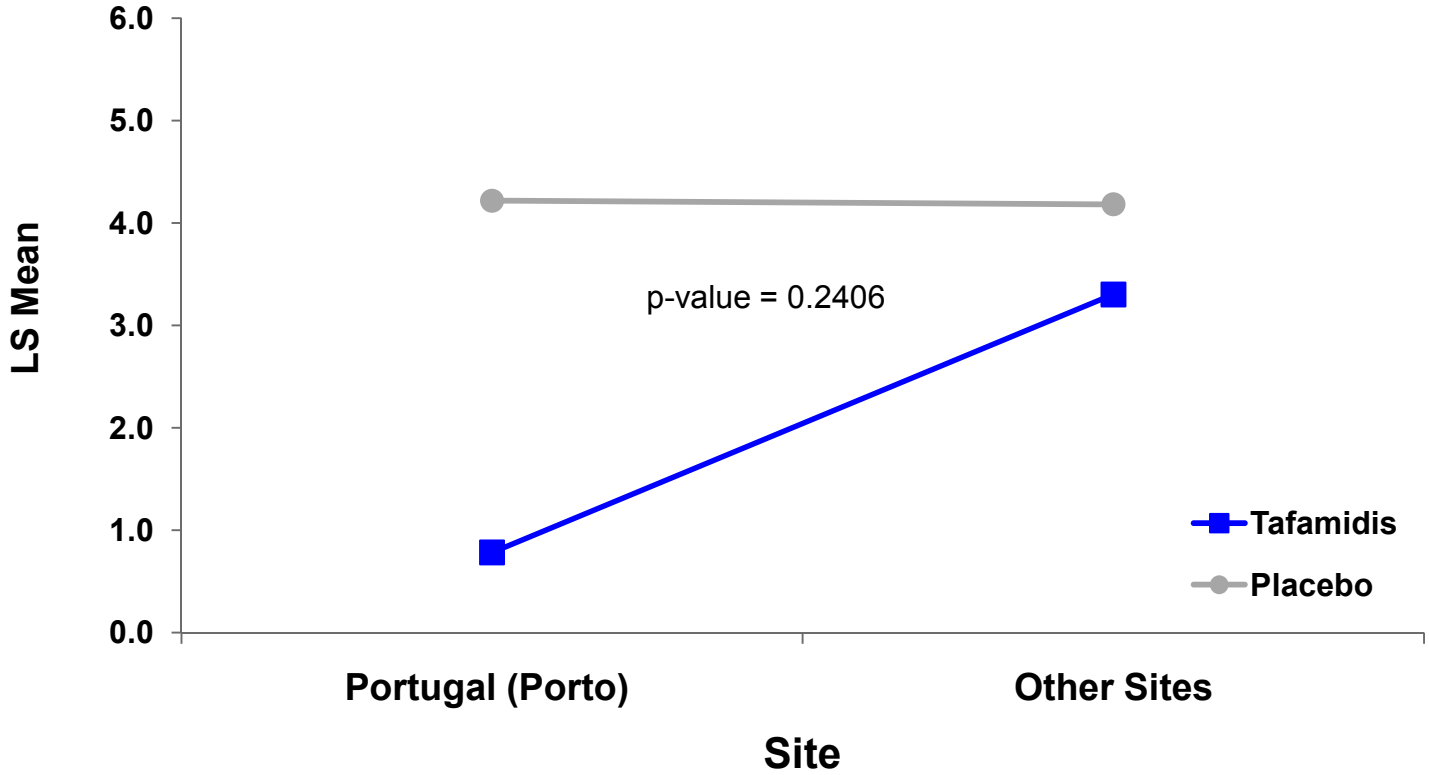
Change from Baseline in Efficacy Endpoints at Month 6 in Subjects who Discontinued due to Liver Transplant



Tafamidis n= 9 Placebo n= 9

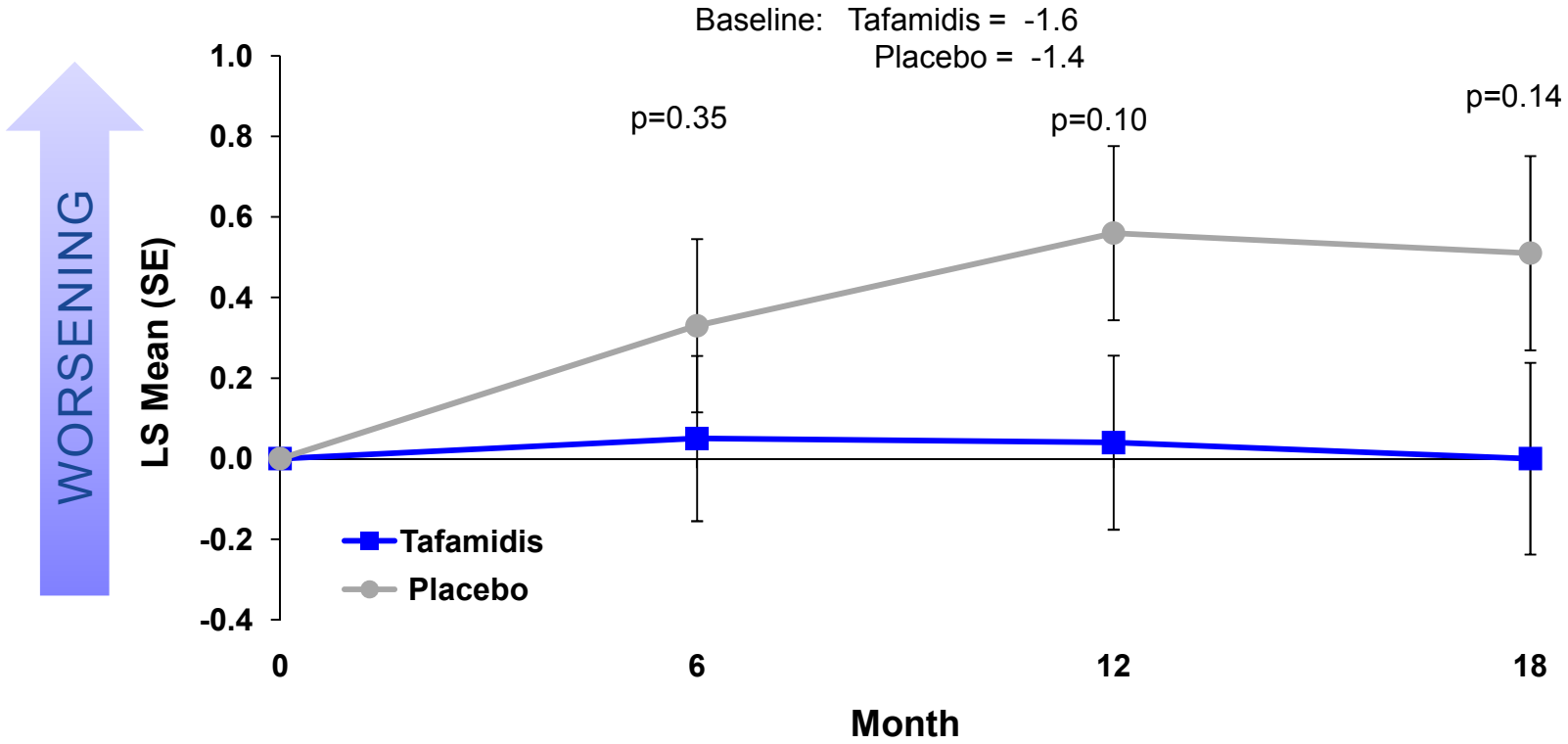
E274

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 variabables. An unstructured covariance matrix was used

Fx-005 HRDB Normal Deviates
Change from Baseline to Months 6, 12 and 18 (ITT, OC)



Tafamidis N= 64	54	42	41
Placebo N= 61	49	44	41

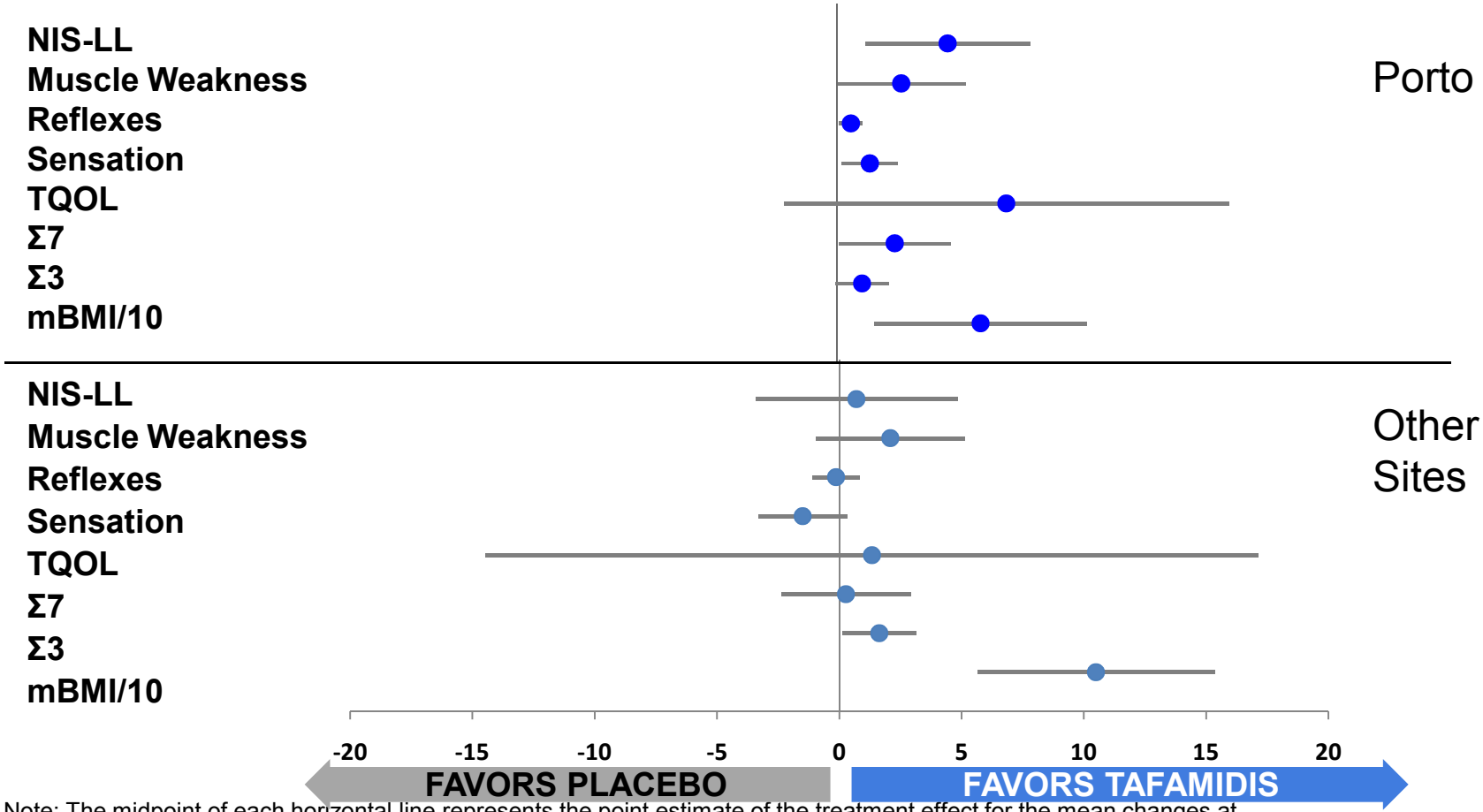
p-values based on repeated measures analysis of variance with change from baseline as the dependent variable, treatment, month and treatment x month as fixed effects, subject as a random effect, and an unstructured covariance matrix."

E416

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)

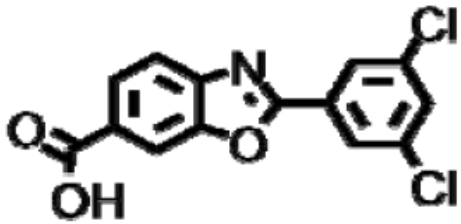


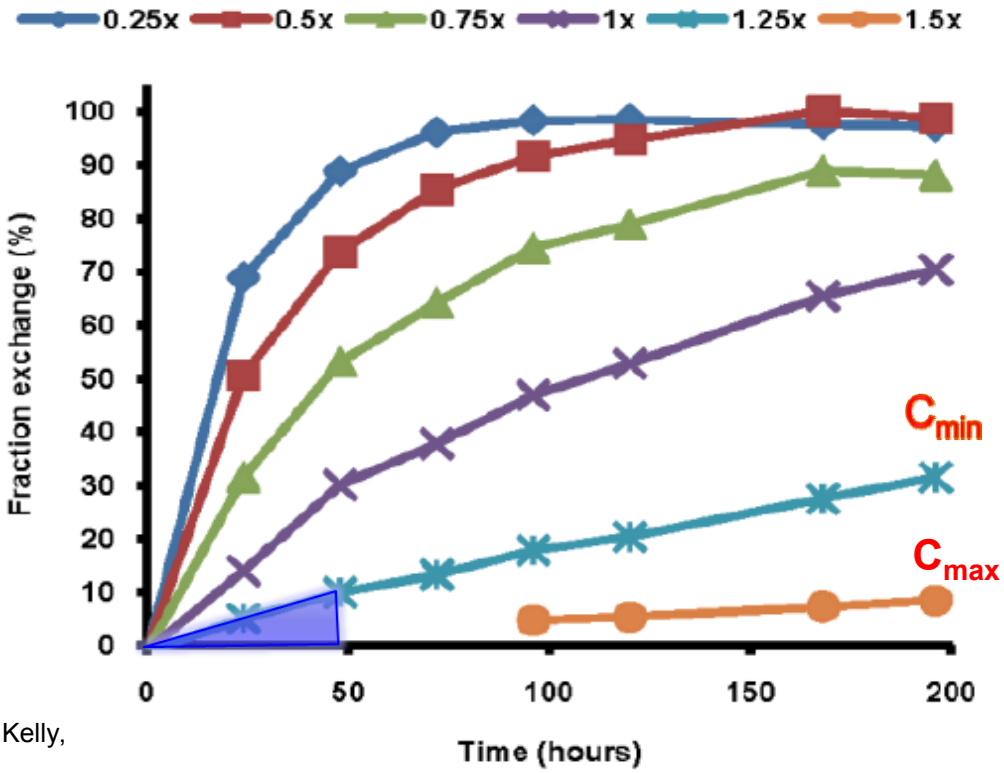
Note: The midpoint of each horizontal line represents the point estimate of the treatment effect for the mean changes at Month 18 for each endpoint; the limits represent the 95% confidence intervals about the point estimates.

AH1

Tafamidis Stabilizes TTR Under Physiological Conditions

Tafamidis; K_{d1}= 2 nM; K_{d2}= 154 nM





Bulawa, C.E.; Connelly, S.; DeVit, M.; Wang, L. Weigel, C.;Fleming, J. Packman, J.; Powers, E.T.; Wiseman, R.L.; Foss, T.R.; Wilson, I.A.; Kelly, J.W.; Labaudiniere, R. *Proc. Natl. Acad. Sci.* 2012 *in press*