The landscape of ATTR amyloidosis treatment

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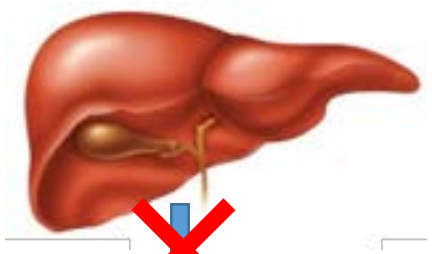
Disclosures

- Hospital Santo António was paid per protocol for clinical trials from FoldRx, Pfizer, Ionis and Alnylam and received grants from FoldRx and Pfizer.

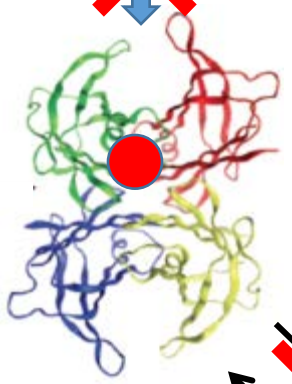
- Dr Coelho received support from Pfizer, Ionis, Biogen and Alnylam to attend scientific meetings.

- Dr Coelho has presented on behalf of Pfizer, Alnylam, Glaxo, Prothena and Ionis/Akcea and received honoraria.

Therapeutic approaches

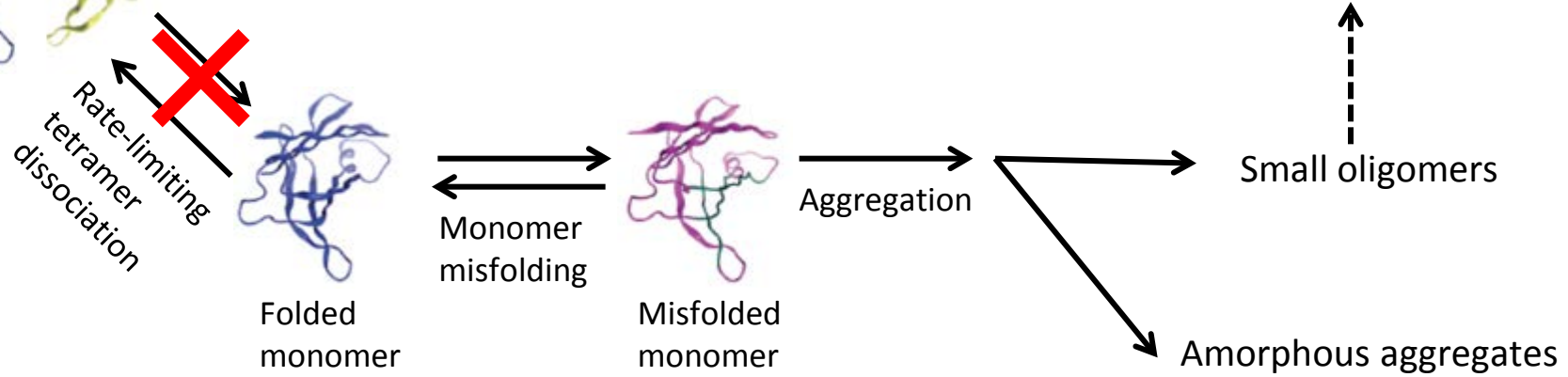


Suppression of the synthesis
- Liver transplantation
- Gene silencing (siRNA, ASO)



Tetramer stabilizers
- Tafamidis
- Diflunisal
- Others

Amyloid fibril degradation/reabsorption
- EGCG
- Doxycycline + TUDCA
- Anti-SAP therapy
- Anti-amyloid Ab
- Molecular tweezers



Redirecting oligomers off-pathway

ASO, antisense oligonucleotide; EGCG, epigallocatechin gallate; SAP, serum amyloid P component; TUDCA, tauroursodeoxycholic acid

This presentation:

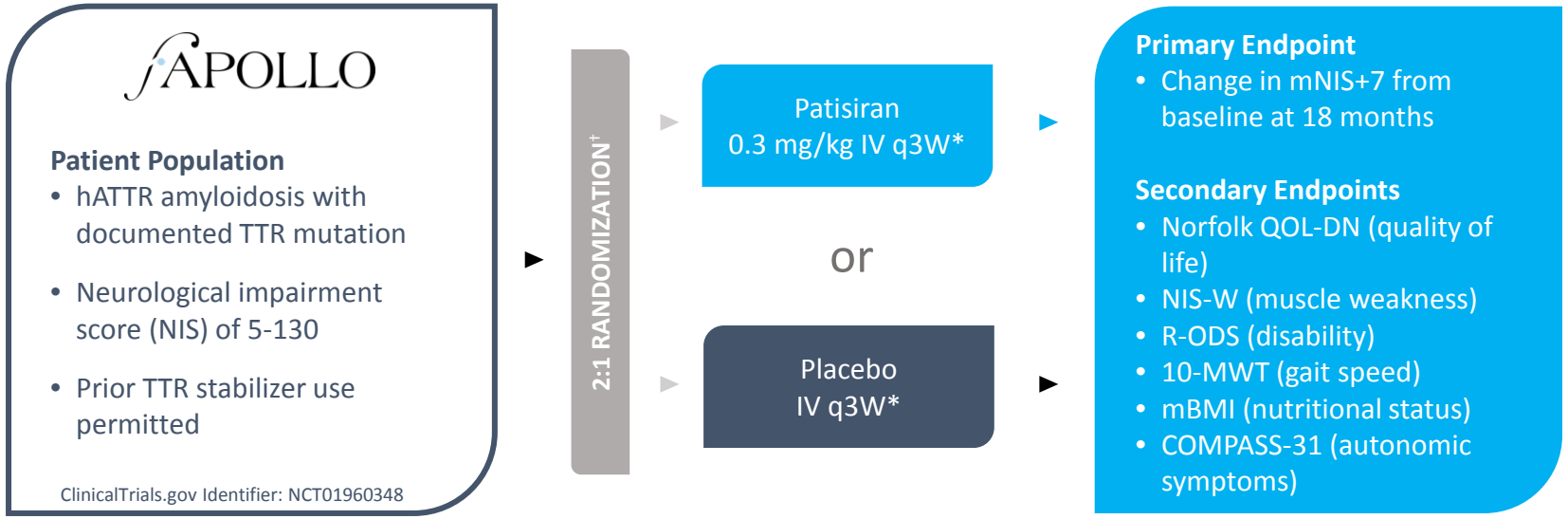
1. The recently published results of the two double blind, randomized, placebo controlled, multicentre clinical trials, with experimental drugs that knockdown plasma transthyretin (TTR), Inotersen and Patisiran.
2. The recent published results of the double blind, randomized, placebo-controlled, multicentre clinical trial with Tafamidis in two different doses (20 and 80 mg) for the treatment of ATTR cardiomyopathy.
3. Real world data on Tafamidis efficacy and safety.
   - Is there a place for Tafamidis after Inotersen and Patisiran approval?
4. Liver transplant for the treatment of ATTR amyloidosis.
   - Lessons from the prolonged survival of ATTR amyloidosis patients.
5. Is Tafamidis able to prevent the development of eye and CNS disease?

Apollo results

Clinical trial with Patisiran

Adams, D., et al., *Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis.* ***N Engl J Med, 2018. 379(1): p. 11-21.***

Patisiran Phase 3 APOLLO Study Design



Primary Endpoint: mNIS+7

- Composite score of polyneuropathy
- Measures: muscle strength/weakness, quantitative sensory testing, muscle stretch reflexes, nerve conduction studies, and postural blood pressure

Key Secondary Endpoint: Norfolk QOL-DN

- 35-item QOL questionnaire that is sensitive to small fiber, large fiber, and autonomic nerve function

Patients who completed the study were eligible for patisiran treatment in the Global OLE Study (NCT02510261)

†Stratification factors for randomization include: neuropathy impairment score (NIS: < 50 vs. ≥ 50), early onset V30M (< 50 years of age at onset) vs. all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs. no previous use.
*To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol; H2 blocker (e.g., ranitidine or famotidine); and H1 blocker (e.g., diphenhydramine).

COMPASS-31, composite autonomic symptom score-31; 10-MWT, 10-meter walk test; mBMI, modified body mass index; mNIS+7, modified neuropathy impairment scale +7; Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire; OLE, open-label extension; q3W, every 3 weeks; R-ODS; Rasch-built overall disability scale

Adams D et al. BMC Neurol. 2017;17(1):181; Adams D, et al.. N Engl J Med 2018;379:11-21; 5

Patisiran Phase 3 APOLLO Study Results

Baseline Demographics and Disease Characteristics

Demographic, n (%)	Placebo (N=77)	Patisiran (N=148)
Median age, years (range)	63 (34, 80)	62 (24, 83)
Gender, males	58 (75.3)	109 (73.6)
Race*		
Asian	**25 (32.5)**	27 (18.2)
Black/African or African American	1 (1.3)	4 (2.7%)
White/Caucasian	50 (64.9)	**113 (76.4)**
Region†		
North America	10 (13.0)	**37 (25.0)**
Western Europe	36 (46.8)	62 (41.9)
Rest of World	31 (40.3)	49 (33.1)
hATTR diagnosis		
Years since hATTR diagnosis, mean (min, max)	2.60 (0.0, 16.5)	2.39 (0.0, 21.0)
TTR genotype		
V30M	**40 (51.9)**	56 (37.8)
nonV30M‡	37 (48.1)	**92 (62.2)**
Previous TTR tetramer stabilizer use	41 (53.2)	78 (52.7)

Disease Characteristics, n (%)	Placebo (N=77)	Patisiran (N=148)
FAP stage		
1: Unimpaired ambulation	37 (48.1)	67 (45.3)
2: Assistance with ambulation required	39 (50.6)	81 (54.7)
3: Wheelchair bound or bedridden	1 (1.3)	0
PND score		
I: Preserved walking, sensory disturbances	20 (26.0)	36 (24.3)
II: Impaired walking but can walk without stick or crutch	23 (29.9)	43 (29.1)
IIIa: Walk with 1 stick or crutch	22 (28.6)	41 (27.7)
IIIb: Walk with 2 sticks or crutches	11 (14.3)	28 (18.9)
IV: Confined to wheelchair or bedridden	1 (1.3)	0
Cardiac subpopulation♯	36 (46.8)	**90 (60.8)**

Blue, bolded text indicated >10% difference in either group

*Other, patisiran N=1 (0.7%); More than one race, patisiran N=2 (1.4%); missing N=1 each for placebo (1.3%) and patisiran (0.7%)

†North America: USA, CAN; Western Europe: DEU, ESP, FRA, GBR, ITA, NLD, PRT, SWE; Rest of world: Asia: JPN, KOR, TWN, Eastern Europe: BGR, CYP, TUR; Central & South America: MEX, ARG, BRA

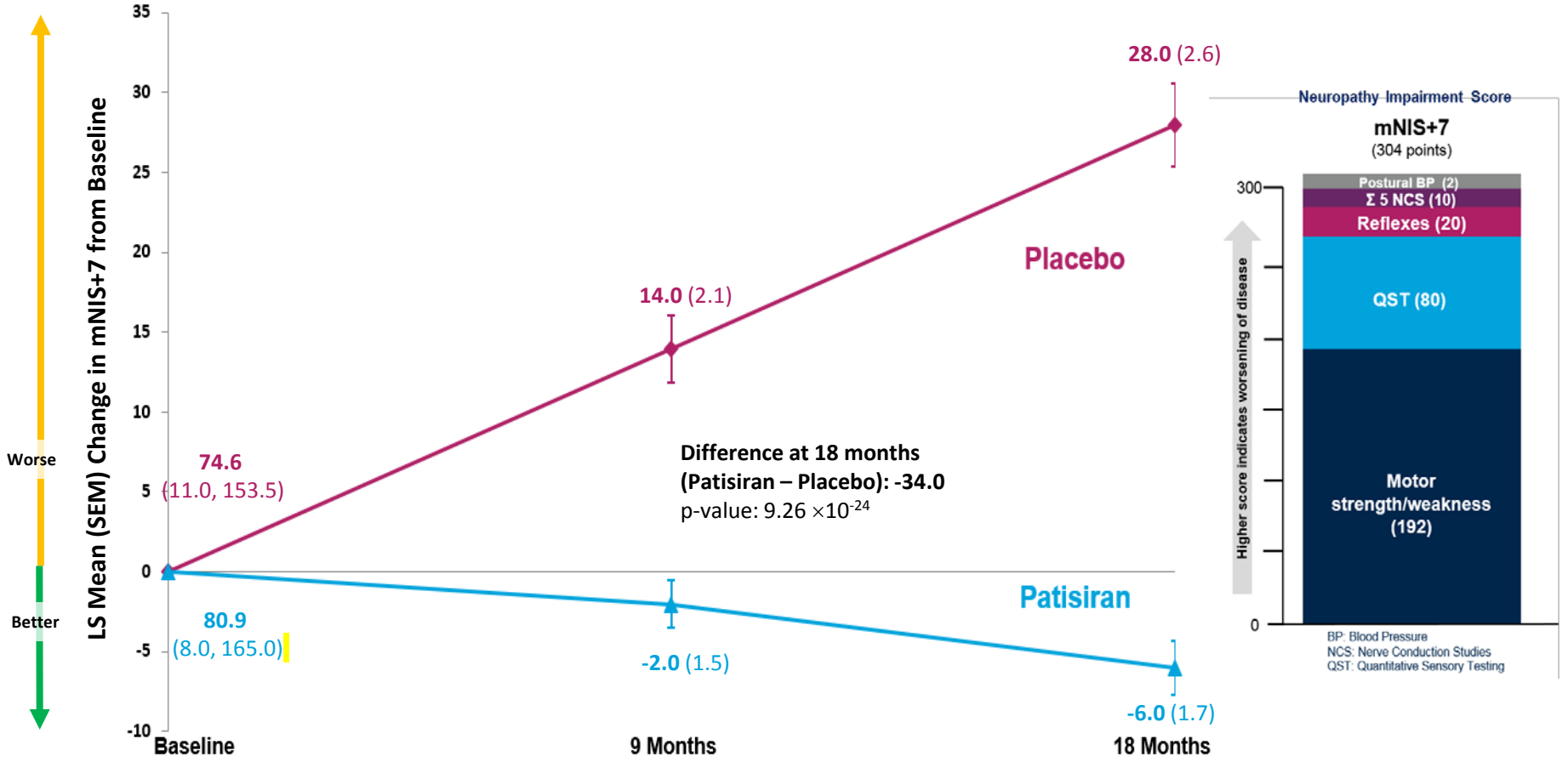
‡Represents 38 different TTR mutations

♯Pre-specified cardiac subpopulation: patients with evidence of pre-existing cardiac amyloid involvement at baseline without confounding medical conditions (i.e., patients with baseline left ventricular [LV] wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history)

Adams D, et al.. N Engl J Med 2018;379:11-21; 5

Patisiran Phase 3 APOLLO Study Results

mNIS+7: Change from Baseline



56.1% of patients in the patisiran group demonstrated improvement in mNIS+7 compared to 3.9% of patients on placebo
(odds ratio: 39.9; p=1.82 x 10^{-15}; improvement defined as <0 point increase from baseline to 18 months)

mNIS+7, modified neuropathy impairment score + 7; LS, least squares; SEM, standard error of the mean; mNIS+7 reference range: 0-304 points
Adams D, et al.. N Engl J Med 2018;379:11-21; 5

Patisiran Phase 3 APOLLO Study Results

Safety and Tolerability

Type of Adverse Event, number of patients (%)	Placebo (N=77)	Patisiran (N=148)
Adverse event (AE)	75 (97.4)	143 (96.6)
Severe AE	28 (36.4)	42 (28.4)
Serious adverse event (SAE)	31 (40.3)	54 (36.5)
AE leading to treatment discontinuation	11 (14.3)	7 (4.7)
AE leading to study withdrawal	9 (11.7)	7 (4.7)
Death	6 (7.8)	7 (4.7)

No deaths considered related to study drug

- Causes of death consistent with natural history

Majority of AEs were mild or moderate in severity

- Peripheral edema
  - Decreased over time
  - Did not result in any treatment discontinuations
- Infusion-related reactions (IRRs)
  - Majority mild in severity
  - Decreased over time
  - 1 patient discontinued treatment

No safety signals regarding liver function tests, hematology including thrombocytopenia, or renal dysfunction related to patisiran

Adverse Events Occurring in ≥ 10% in Either Group

Preferred AE Term, number of patients (%)	Placebo (N=77)	Patisiran (N=148)
Diarrhea	29 (37.7)	55 (37.2)
Edema, peripheral	17 (22.1)	**44 (29.7)**
IRRs	7 (9.1)	**28 (18.9)**
Fall	**22 (28.6)**	25 (16.9)
Constipation	13 (16.9)	22 (14.9)
Nausea	**16 (20.8)**	22 (14.9)
Dizziness	11 (14.3)	19 (12.8)
Urinary tract infection	**14 (18.2)**	19 (12.8)
Fatigue	8 (10.4)	18 (12.2)
Headache	9 (11.7)	16 (10.8)
Cough	9 (11.7)	15 (10.1)
Insomnia	7 (9.1)	15 (10.1)
Nasopharyngitis	6 (7.8)	15 (10.1)
Vomiting	8 (10.4)	15 (10.1)
Asthenia	9 (11.7)	14 (9.5)
Pain in Extremity	8 (10.4)	10 (6.8)
Muscular Weakness	**11 (14.3)**	5 (3.4)
Anemia	**8 (10.4)**	3 (2.0)
Syncope	**8 (10.4)**	3 (2.0)

Blue, bolded text: Indicates ≥5 percentage point difference in either group

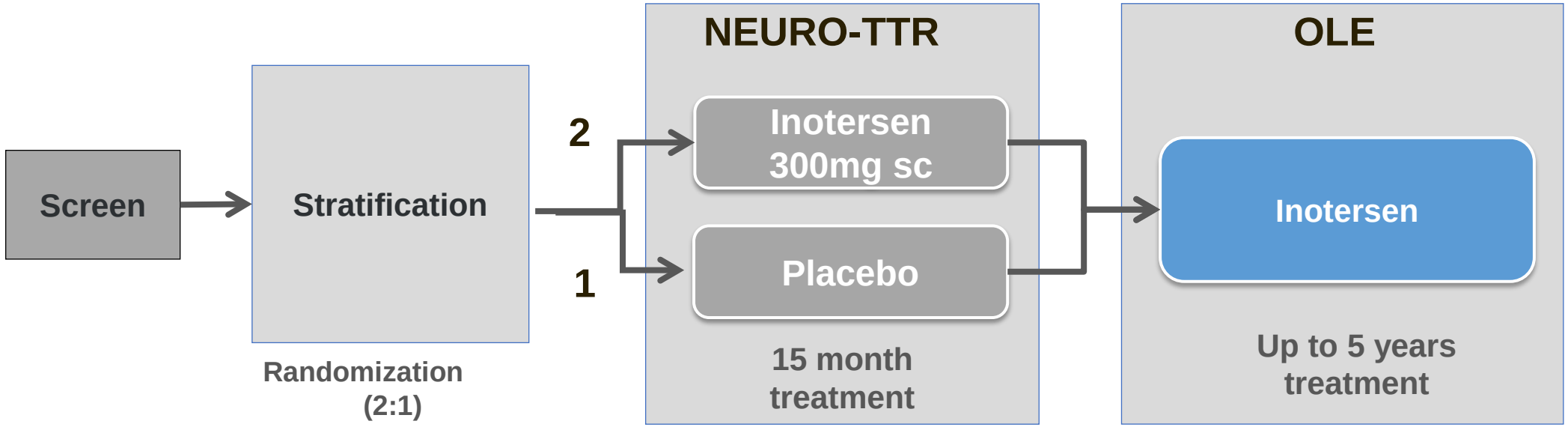
Adams D, et al.. N Engl J Med 2018;379:11-21; 5

Neuro-TTR results

Clinical trial with Inotersen

Benson, M.D., et al., *Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis.* ***N Engl J Med, 2018. 379(1): p. 22-31.***

NEURO-TTR: A Phase 3 Study of Inotersen in Patients with hATTR-PN



- Stratification:
  - Stage 1 vs. Stage 2
  - V30M TTR mutation vs. non-V30M TTR mutation
  - Previous treatment with either tafamidis or diflunisal vs. no known previous treatment
- Primary endpoints:
  - Modified Neuropathy Impairment Score +7 (mNIS+7)
  - Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QOL-DN)

Baseline Demographics

All patients	Placebo (n = 60)	Inotersen (n = 112)	Total (N = 172)
Age, mean (SD), years	59.5 (14.1)	59.0 (12.5)	59.2 (13.0)
Sex, male, n (%)	41 (68.3)	77 (68.8)	118 (68.6)
Val30Met, n (%)[a]	33 (55.0)	56 (50.0)	89 (51.7)
Non-Val30Met, n (%)[a]	27 (45.0)	56 (50.0)	83 (48.3)
Disease stage 1, n (%)[a]	42 (70.0)	74 (66.1)	116 (67.4)
Disease stage 2, n (%)[a]	18 (30.0)	38 (33.9)	56 (32.6)
Previous use of stabilizers, n (%)[a,b]	36 (60.0)	63 (56.3)	99 (57.6)
Treatment naive, n (%)[a]	24 (40.0)	49 (43.8)	73 (42.4)
mNIS+7 composite score, mean (SD)	74.8 (39.0)	79.2 (37.0)	77.6 (37.6)
Norfolk QoL-DN total score, mean (SD)	48.7 (26.7)	48.2 (27.5)	48.4 (27.2)

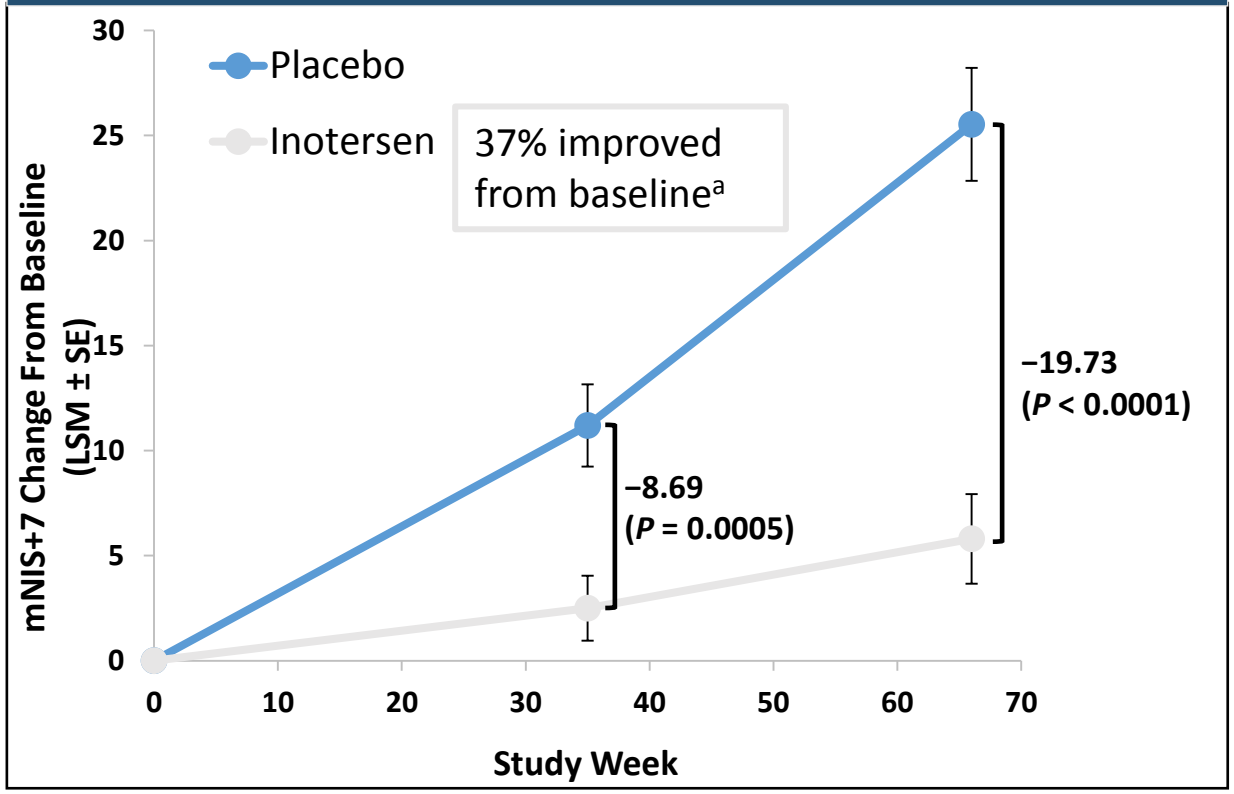
mNIS+7, modified Neuropathy Impairment Score +7 neurophysiologic tests composite score; Norfolk-QoL-DN, Norfolk quality of life-diabetic neuropathy; SD, standard deviation.

[a]Based on data entered in the electronic case report form.

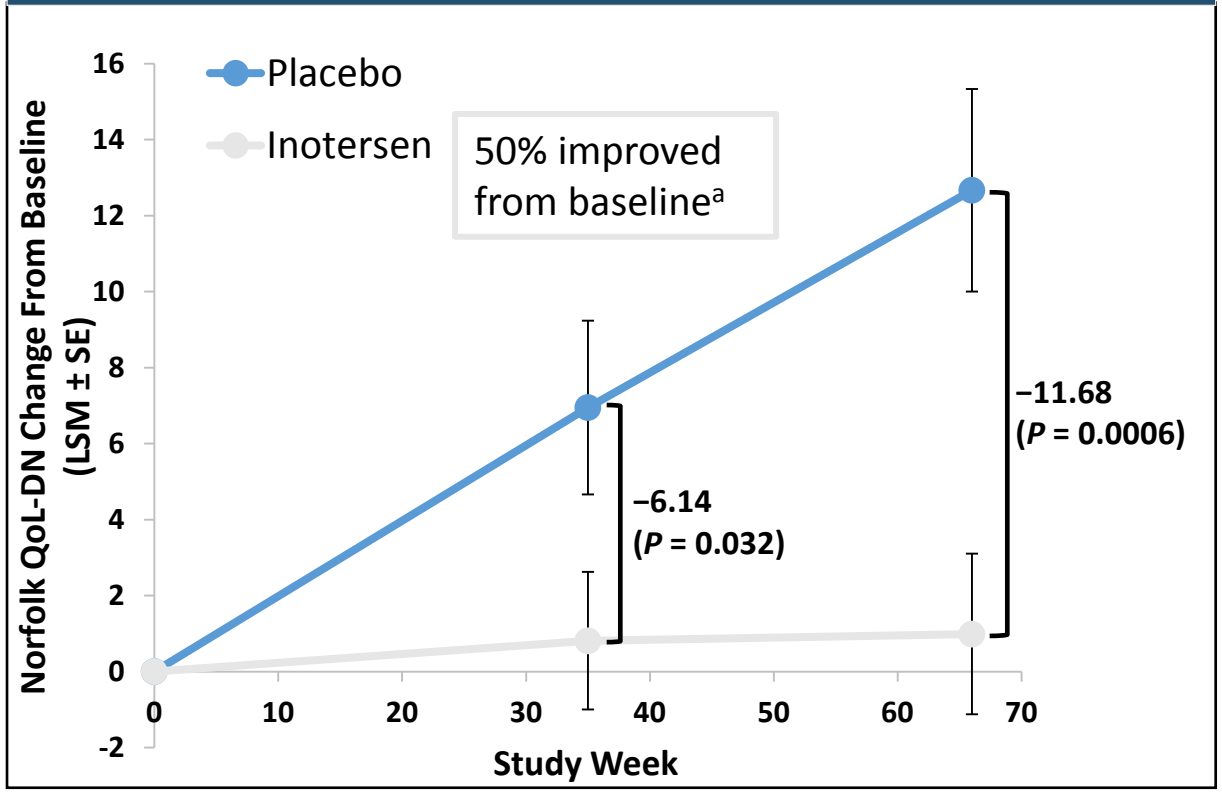
[b]Prior stabilizer use includes tafamidis or diflunisal.

Inotersen-Treated Patients Achieved Significant Benefit in mNIS+7 and Norfolk QoL-DN Total Score and Versus Placebo-Treated Patients

mNIS+7 Composite Score
(measures neuropathy progression)



Norfolk QoL-DN Questionnaire Total Score
(measures the impact of neuropathy on patient-reported QoL)



LSM, least squares mean; mNIS+7, modified Neuropathy Impairment Score +7 neurophysiologic tests composite score; Norfolk-QoL-DN, Norfolk quality of life-Diabetic Neuropathy; QoL, quality of life; SE, standard error.

[a]Population defined as improved includes patients assessed at baseline and week 66 who had score change from baseline to week 66 ≤0 in the end point measure.

Safety Overview

- Most adverse events (AEs) were mild or moderate; safety concerns included thrombocytopenia and glomerulonephritis, which are monitorable and manageable with routine testing
- 36 (32%) inotersen-treated and 13 (22%) placebo-treated patients experienced serious AEs
- 5 (4.5%) deaths occurred, all inotersen-treated patients
  - 4 deaths due to disease progression/underlying disease and 1 due to fatal intracranial hemorrhage associated with serious thrombocytopenia
- 80% of patients completed the 15-month treatment period, and >95% of patients who completed treatment entered the open-label extension study

ATTR-ACT results

Clinical trial with Tafamidis 20 and 80 mg
for the treatment of TTR cardiomyopathy

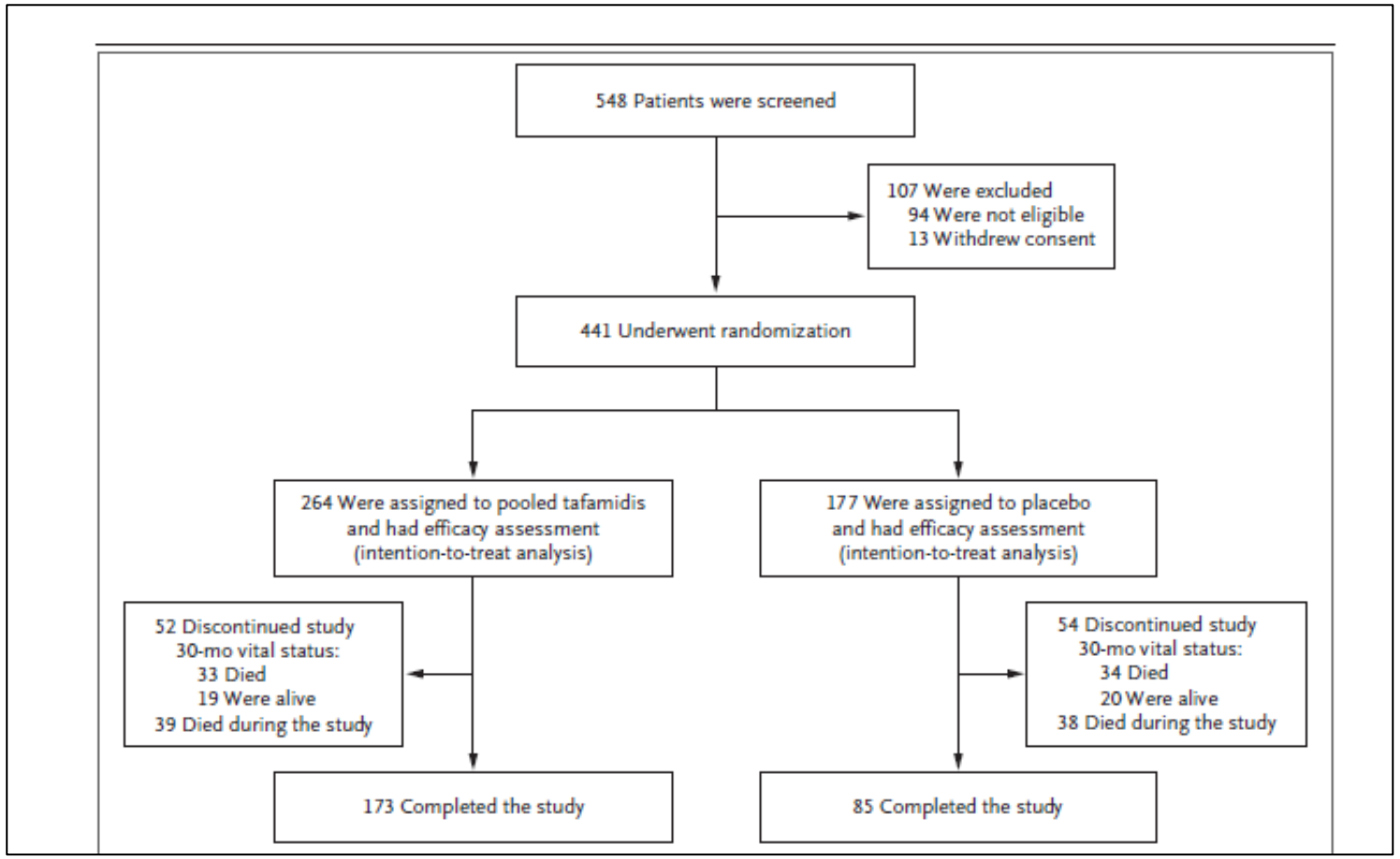
Maurer M., et al., Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy.
N Engl J Med, 2018.

Trial design and patient disposition

Patients with heart failure due to wild or mutant ATTR cardiomyopathy

- Amyloid demonstration in any biopsy
- Mutation detected or excluded according to disease type

- Septal thickness > 12 mm
- NT-proBNP >600
- 6 minute walking test > 100m



Primary outcome measures: Survival analysis and hospitalization risk

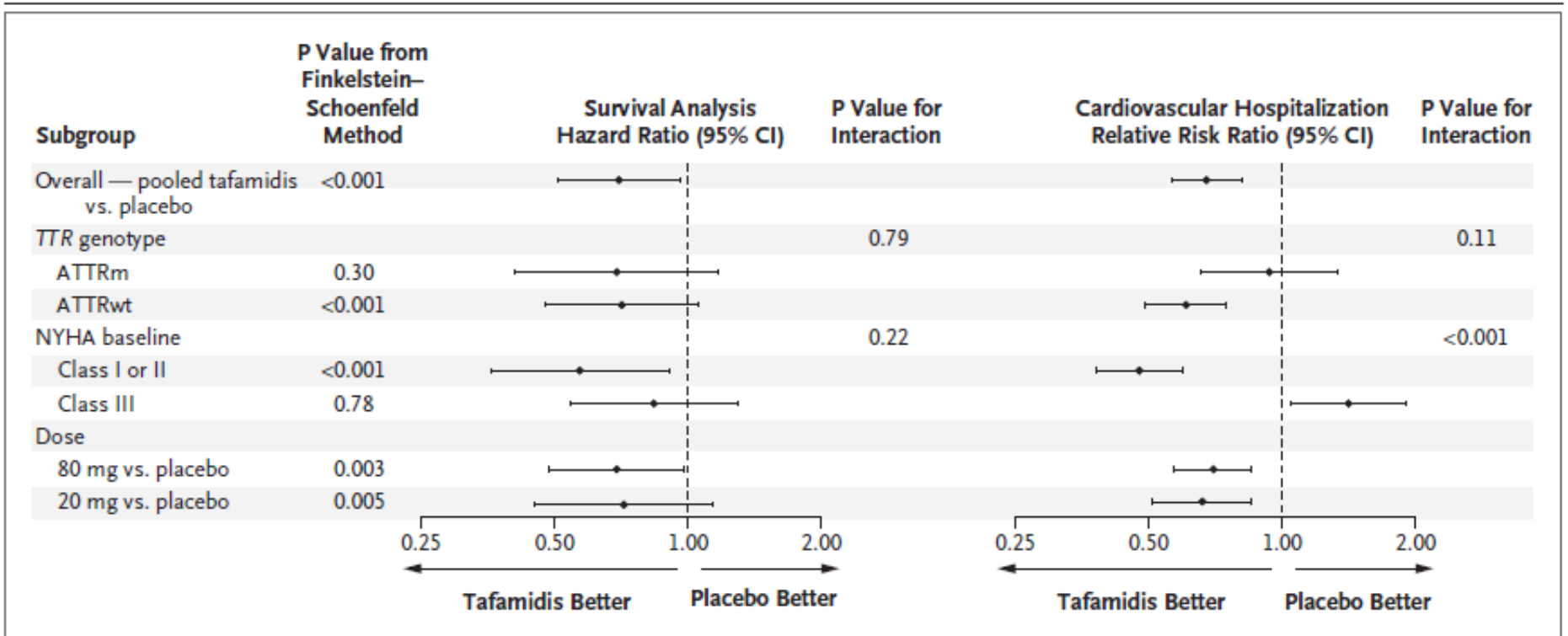
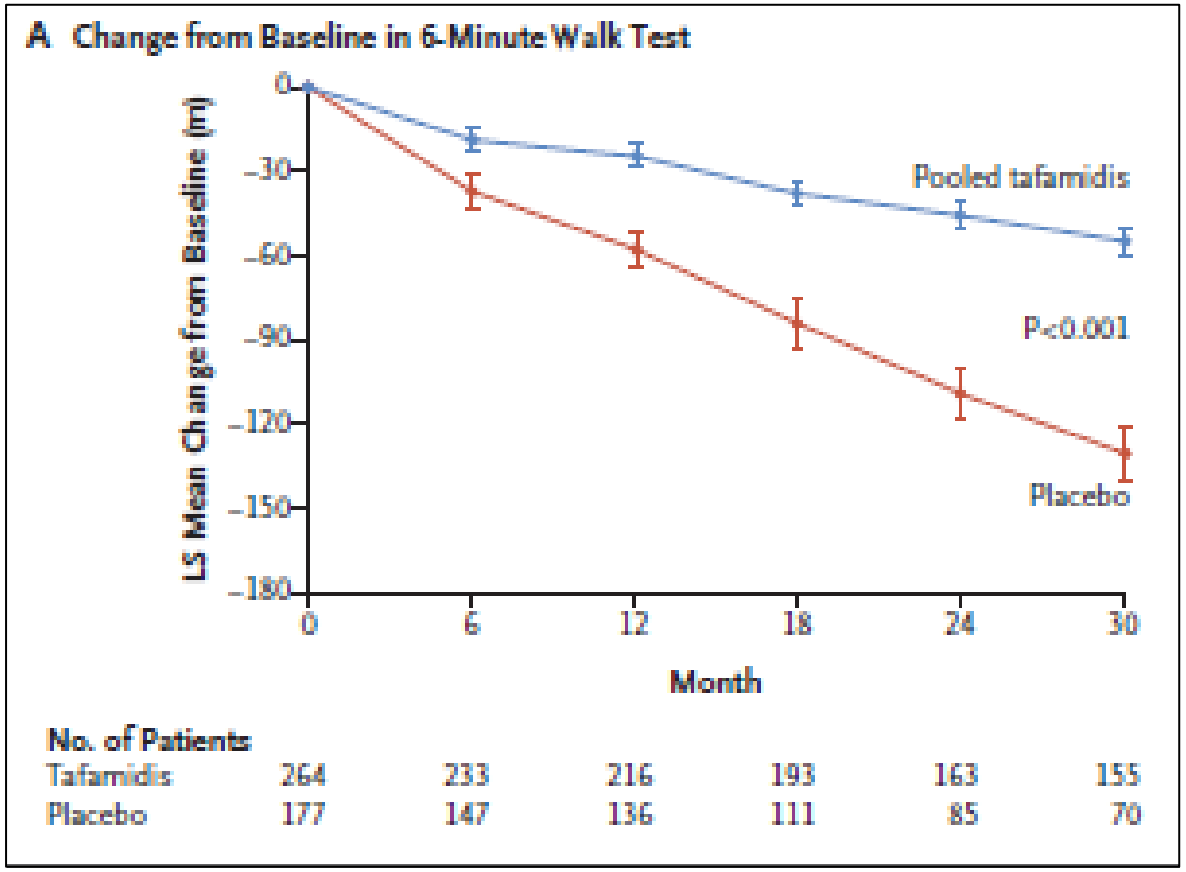
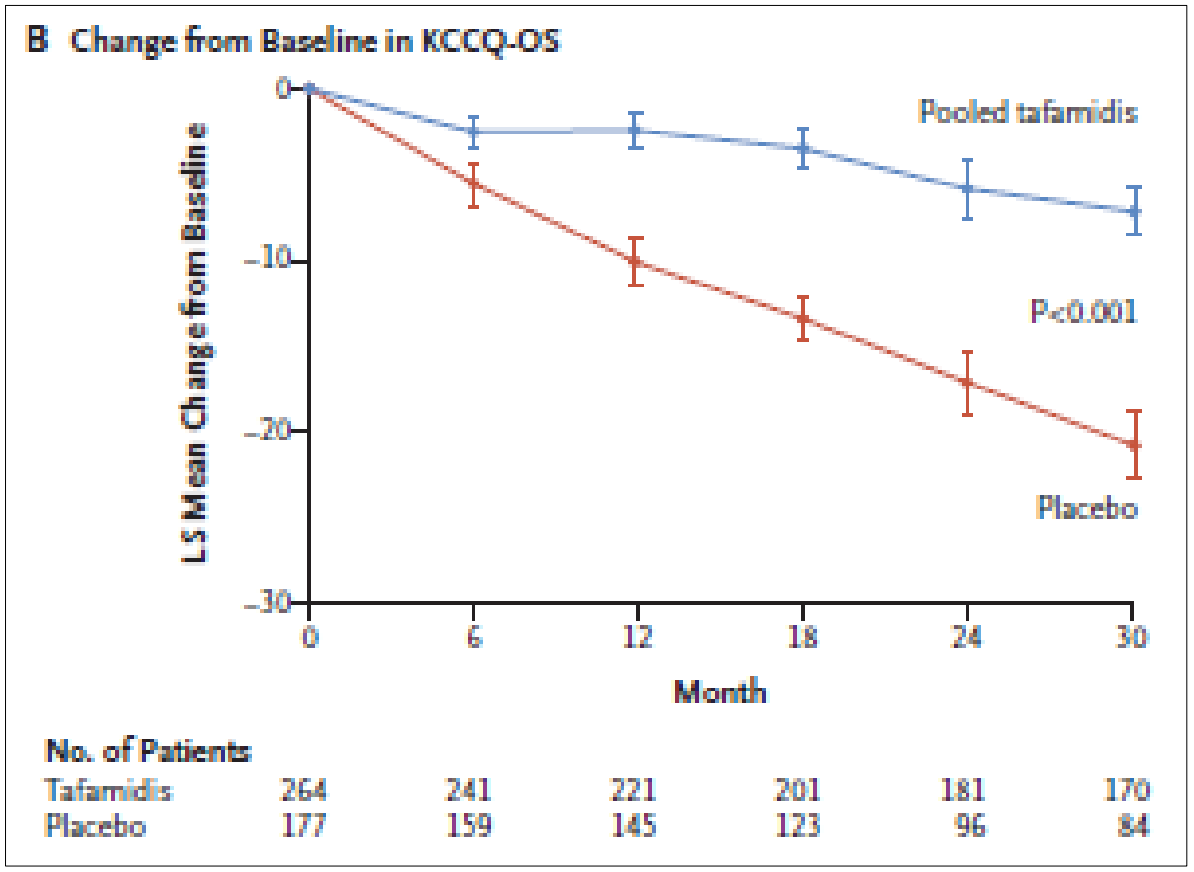


Figure 3. Overall and Subgroup Results as Calculated with the Use of the Finkelstein–Schoenfeld Method, All-Cause Mortality, and Cardiovascular-Related Hospitalizations.

All-cause mortality was evaluated with the use of a Cox proportional-hazards model, with treatment and stratification factors treated as covariates. The survival analysis interaction terms are based on a post hoc analysis. The frequency of cardiovascular-related hospitalizations was assessed with the use of a Poisson regression model. ATTRm denotes disease that results from an inherited autosomal dominant trait that causes pathogenic mutations in *TTR*, ATTRwt disease that results from the deposition of wild-type transthyretin protein, and NYHA New York Heart Association.

Secondary outcome measures: change from baseline in 6-minute walking test and questionnaire score (KCCQ-OS)





Tafamidis

Is there a place for Tafamidis after Inotersen and Patisiran approval?

Tafamidis

Tafamidis, an oral drug that stabilizes transthyretin was approved in Europe in 2011 for the treatment of ATTR-FAP:

- In adult patients;
- With symptomatic polyneuropathy;
- Stage 1 (no need for walking support);
- With any TTR mutation;
- To delay peripheral neurologic impairment.

Recommended dosage: 20 mg capsule once daily.

Treatment should be initiated by and remain under the supervision of a physician knowledgeable in the management of patients with TTR-FAP.

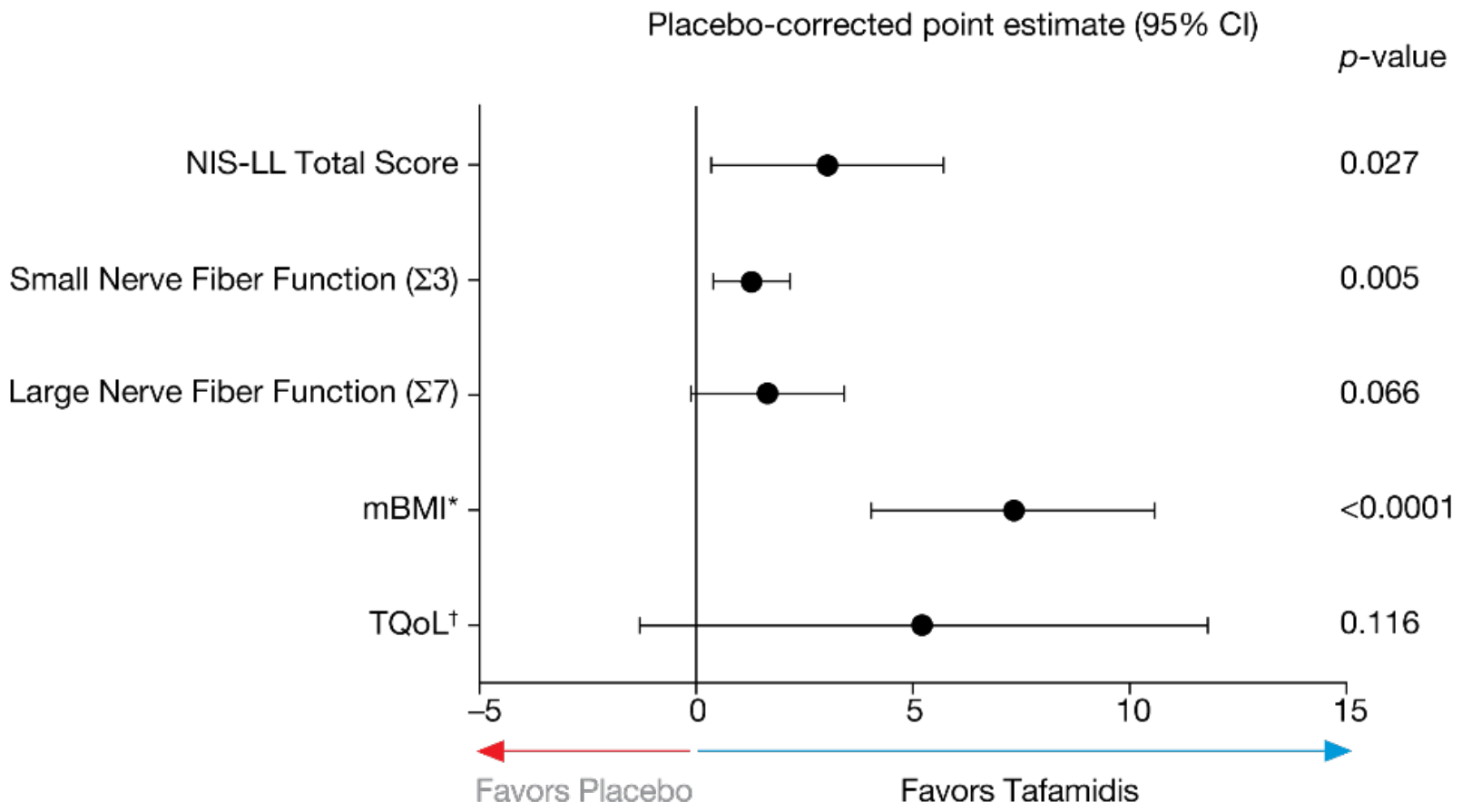
Later approved in Mexico, Argentina, Brazil, Japan and South Korea

Tafamidis clinical trials for ATTR amyloidosis – polyneuropathy

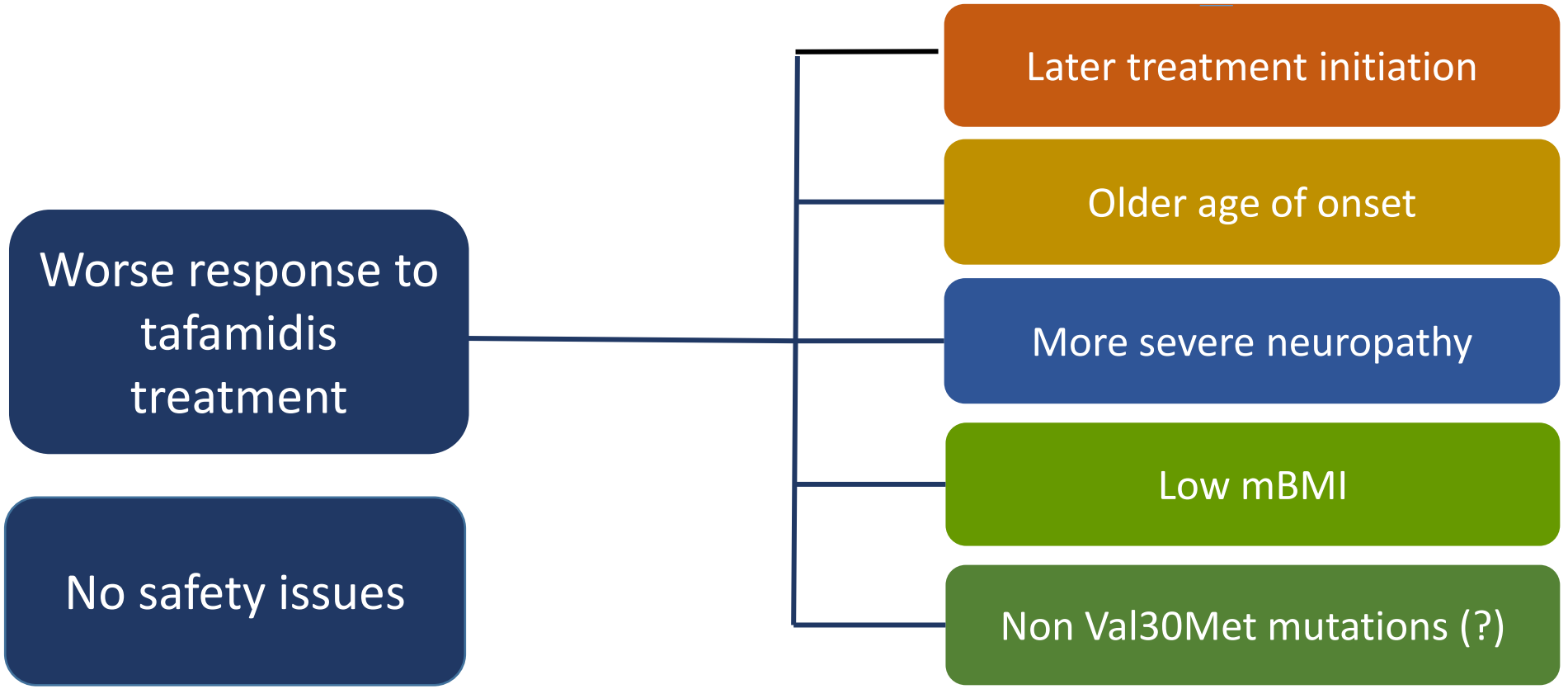
Study Fx-005[1]	Study Fx-006[2]	Study B3461023[4]	Study Fx1A-201[3]
18-month, double-blind, placebo-controlled study	12-month, open-label extension study	Open-label, multicentre study	Open-label, multicentre, 12-month study
Pivotal efficacy study of tafamidis in 128 V30M patients with TTR-FAP	Long-term safety, tolerability, and clinical outcomes study in 86* patients	To assess safety and efficacy at 66 months of tafamidis in V30M and non-V30M patients	Determine TTR stabilisation in patients with mutations other than V30M TTR-FAP
44 Placebo/ 47 tafamidis completed	30 Placebo/ 33 tafamidis completed		17 completed

1. Coelho, T., et al., *Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy.* J Neurol, 2013. **260**(11): p. 2802-14.
2. Coelho, T., et al., *Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial.* Neurology, 2012. **79**(8): p. 785-92.
3. Merlini, G., et al., *Effects of tafamidis on transthyretin stabilization and clinical outcomes in patients with non-Val30Met transthyretin amyloidosis.* J Cardiov Transl Res, 2013. **6**(6): p. 1011-20.
4. Barroso, F.A., et al., *Long-term safety and efficacy of tafamidis for the treatment of hereditary transthyretin amyloid polyneuropathy: results up to 6 years.* Amyloid, 2017. **24**(3): p. 194-204.

Clinical outcomes for measures of disease progression favoured tafamidis[1]



Real life evaluation of Tafamidis treatment (outside Portugal)



1. Lozeron, P., et al., *Effect on disability and safety of Tafamidis in late onset of Met30 transthyretin familial amyloid polyneuropathy.* Eur J Neurol, 2013. **20**(12): p. 1539-45.
2. Cortese, A., et al., *Monitoring effectiveness and safety of Tafamidis in transthyretin amyloidosis in Italy: a longitudinal multicenter study in a non-endemic area.* J Neurol, 2016. **263**(5): p. 916-924.
3. Plante-Bordeneuve, V., et al., *Long-term treatment of transthyretin familial amyloid polyneuropathy with tafamidis: a clinical and neurophysiological study.* J Neurol, 2017. **264**(2): p. 268-276.

Evaluation of Porto experience - Cecília Monteiro, MD

(Collaboration with Kelly's Lab at Scripps Research Institute, La Jolla, California)

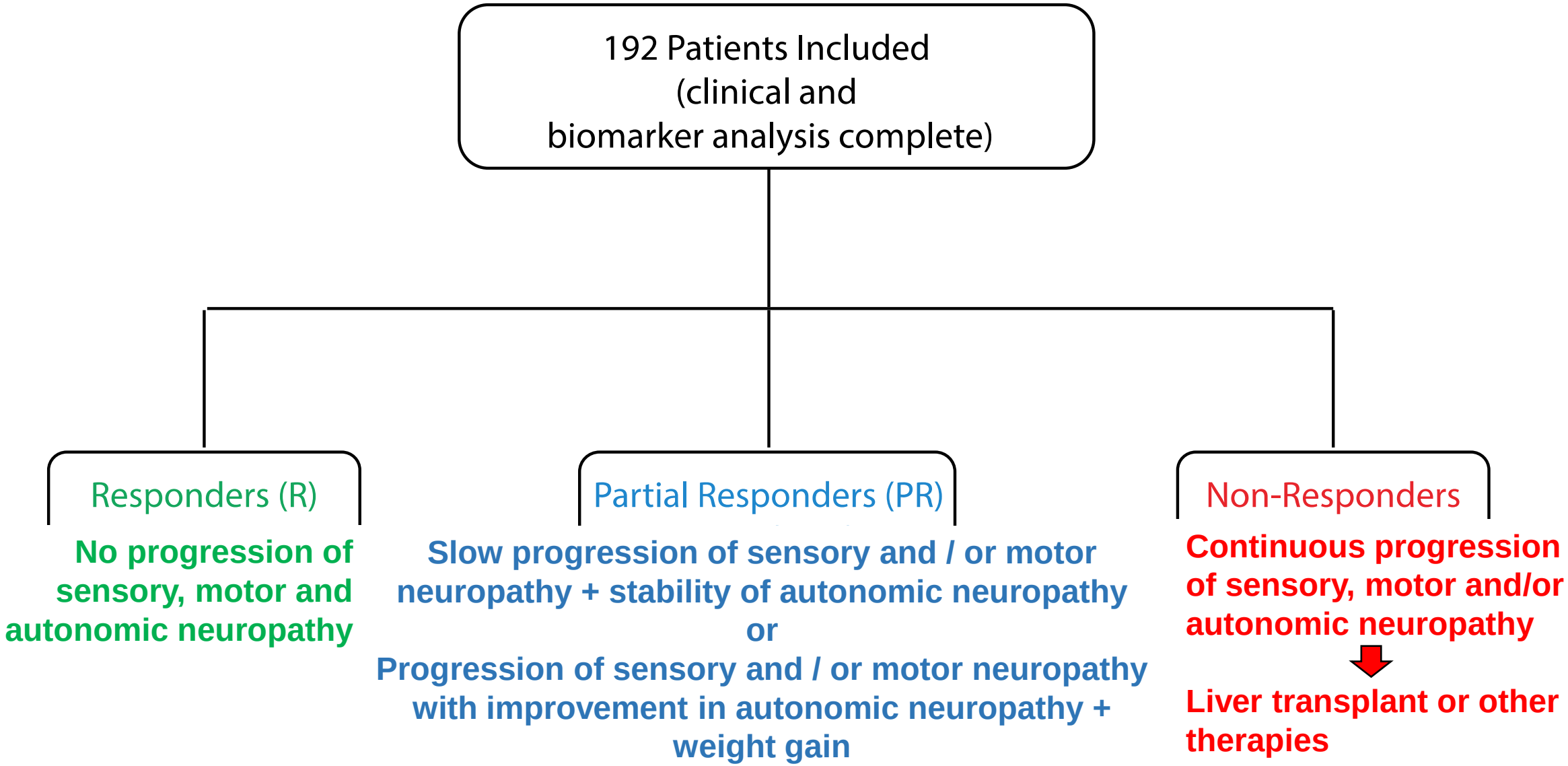
TTRVal30Met	98,4%
Female	46,4%
Age at baseline [median (25th – 75th percentiles)]	36.4 (32.0 – 44.6)
Disease duration [median (25th – 75th percentiles)]	2.1 (1.3 – 3.6)
NIS baseline [median (25th – 75th percentiles)]	8.0 (4.5 – 16.0)

From July 2012 to January 2016
252 patients started Tafamidis

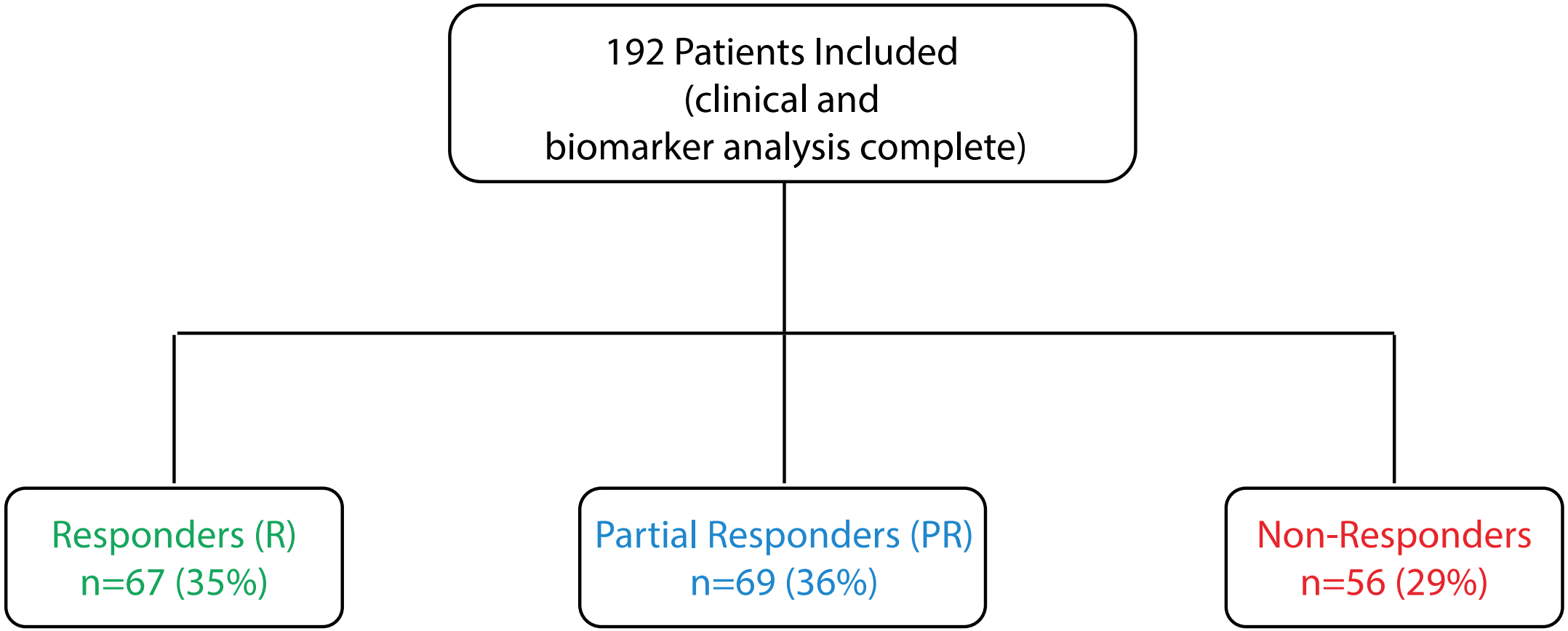
51 excluded
Co-morbidities 19
Treatment interruptions 20
Protocol deviations 5
Add-on-clinical trial 6
Refusal to participate 1

192 patients included in the longitudinal follow-up study fully evaluated

Response to Therapy

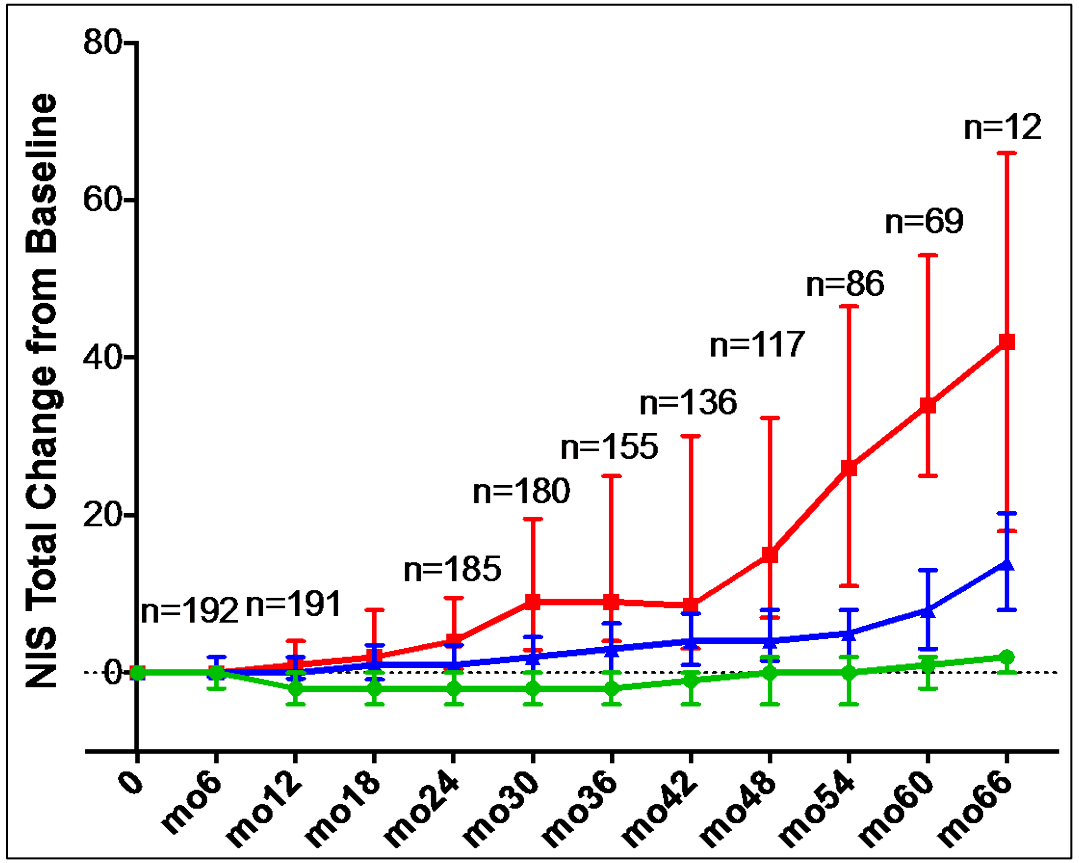


Response to Therapy

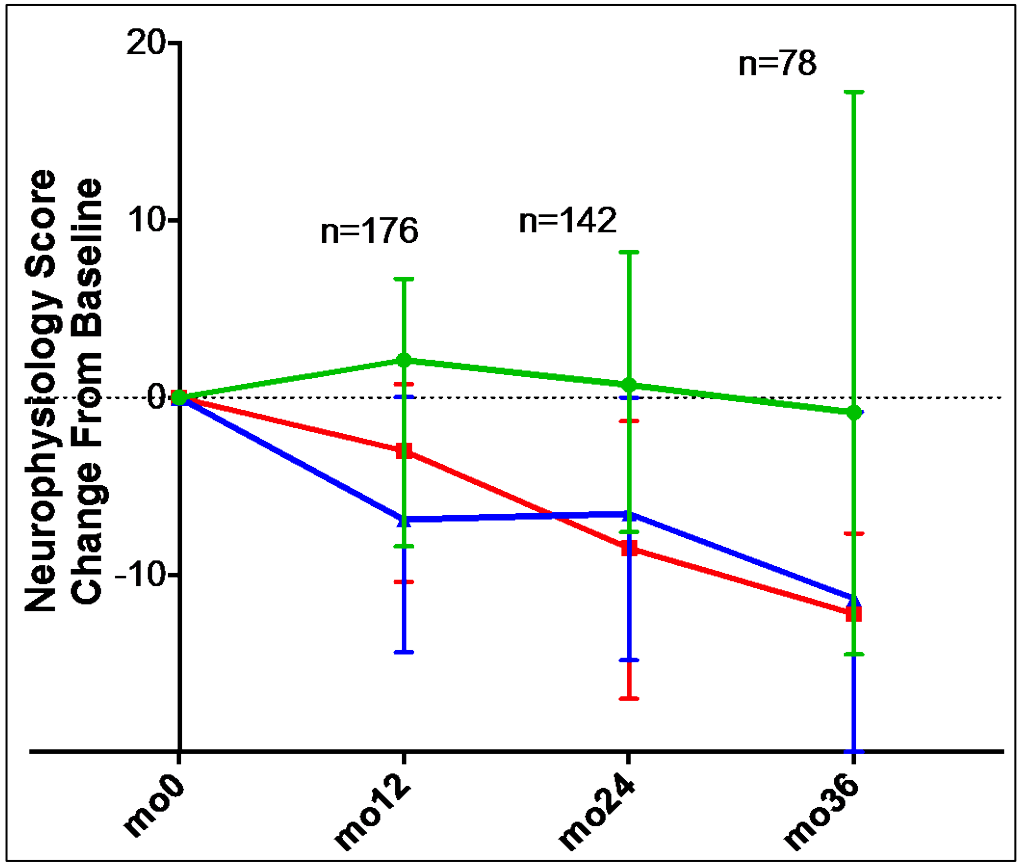


Clinical Outcome Measures Support Clinical Classification as **Responders**, **Partial-Responders** and **Non-Responders**

Neuropathy Impairment Score - Total



Neurophysiology Score *

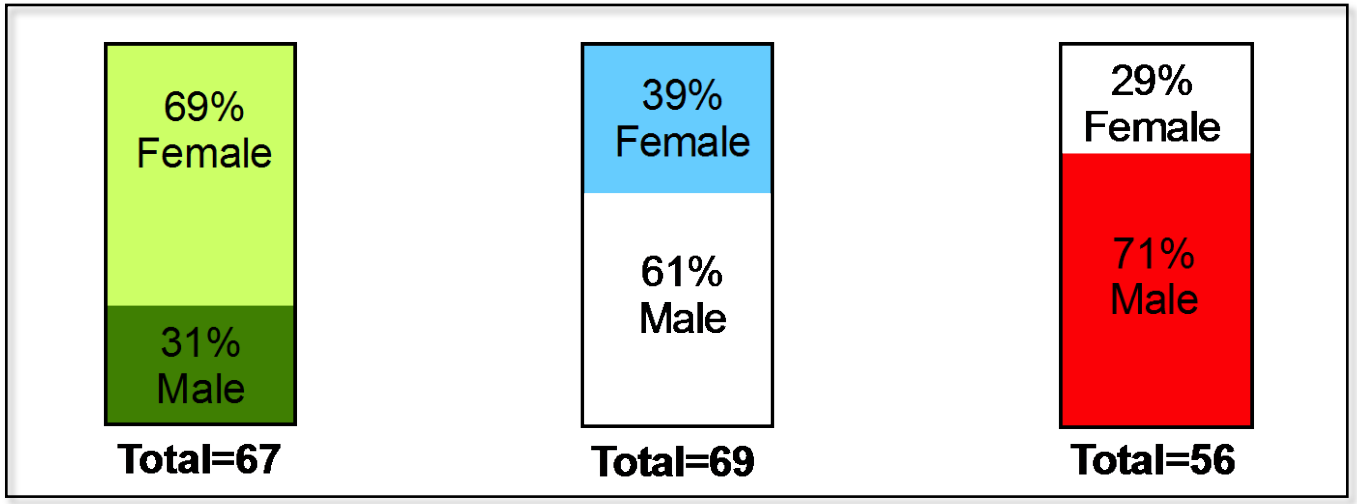


* ∑ 2 SNAP + 3 CMAP (ulnar + sural, and ulnar + peroneal + tibial)

Outcome predictors:

Gender Predicts Outcome to Tafamidis

	Responders (R) N=67	Partial Responders (PR) N=69	Non-Responders (NR) N=56	P-value (R vs PR)	P-value (R vs NR)	P-value (PR vs NR)
Female Gender (n, %)	**46 (69%)**	27 (39%)	16 (29%)	**P<0.0001**	**P<0.0001**	ns



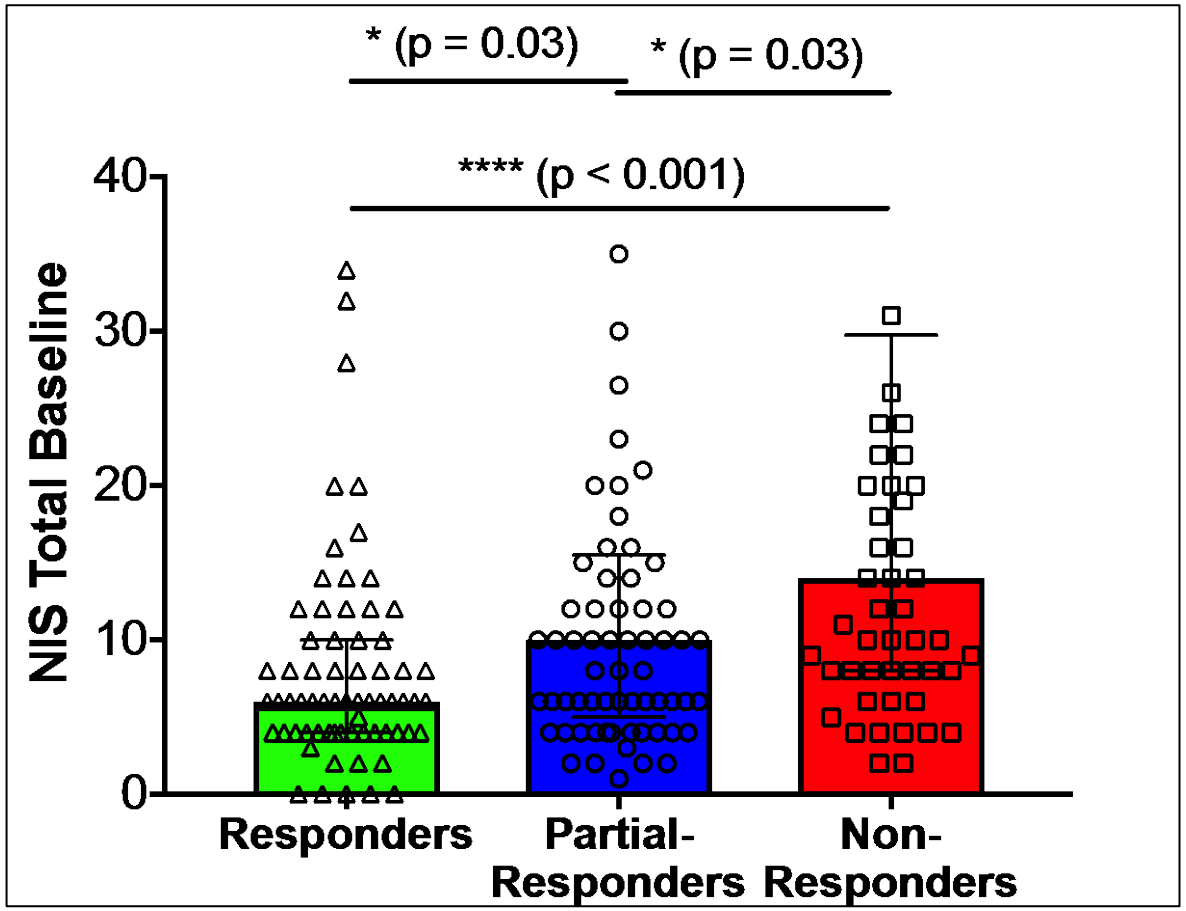
Women are more likely to be **completely stable**

[OR 4.2 (2.1 – 8.3, 95% CI, p<0.0001)]

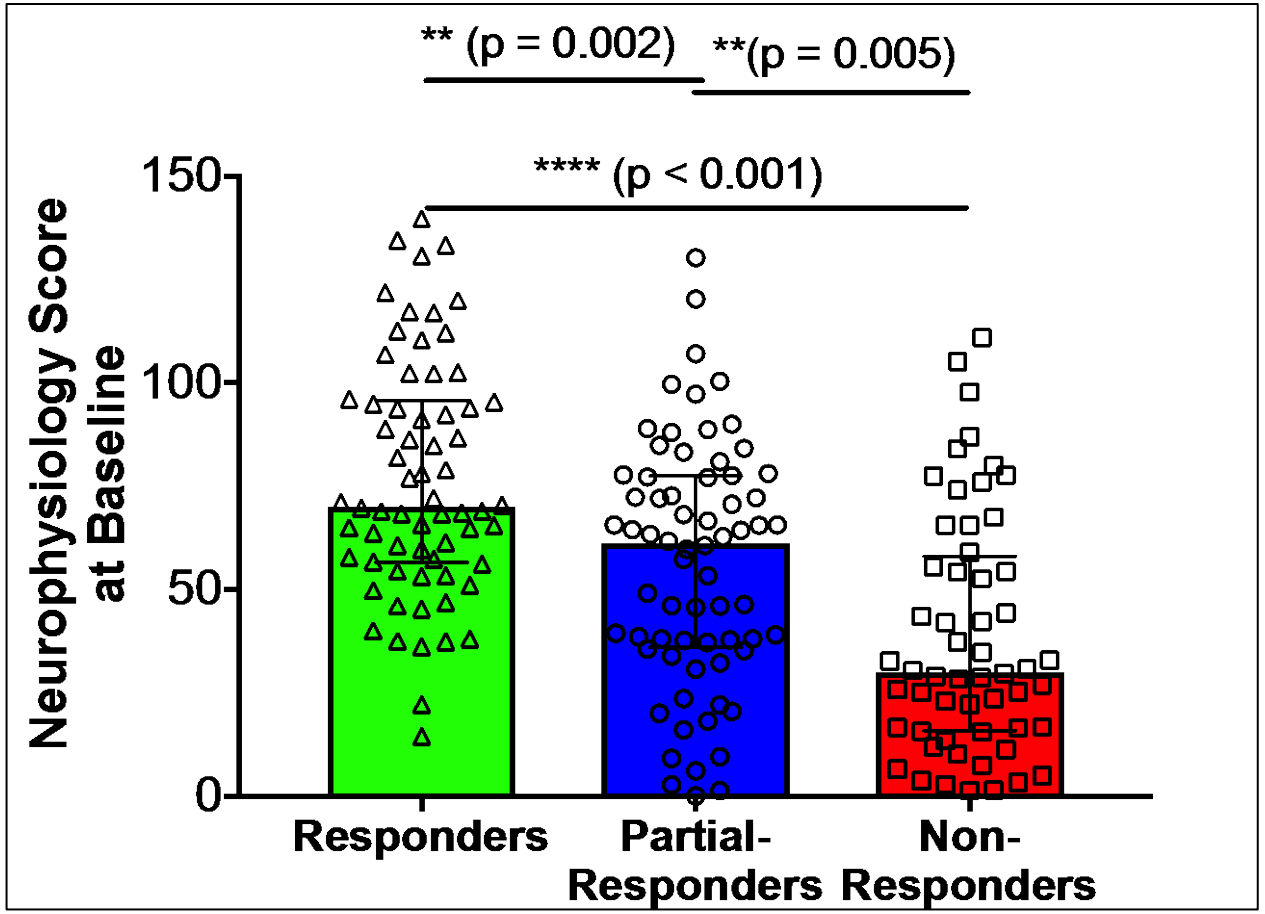
Outcome predictors:

Disease Severity Predicts Outcome to Tafamidis

Neuropathy Impairment Score - Total



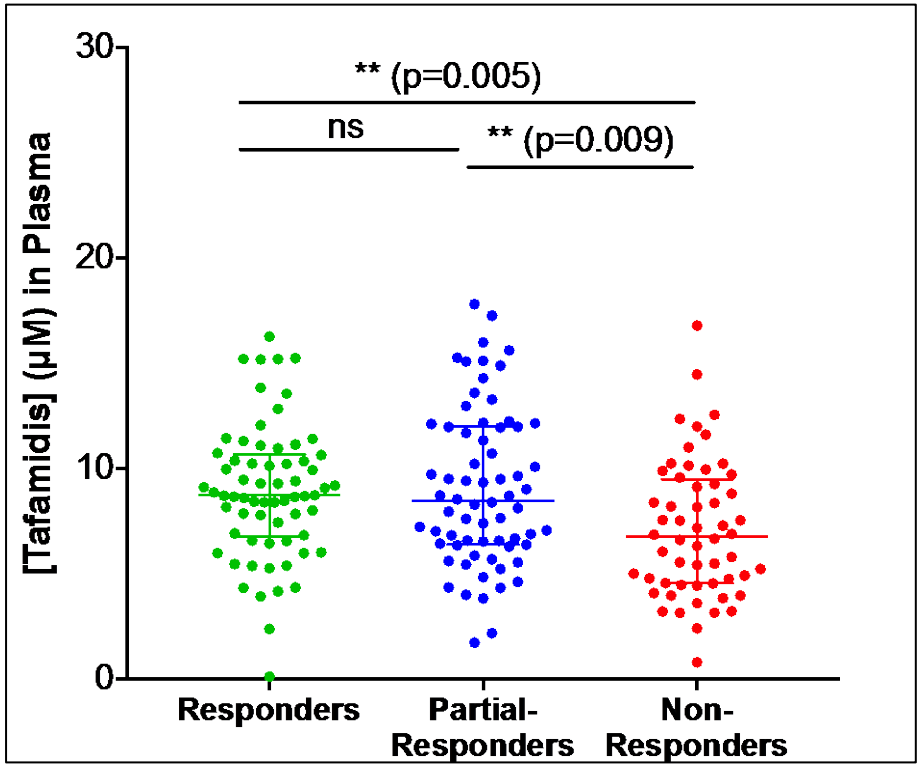
Neurophysiology Score



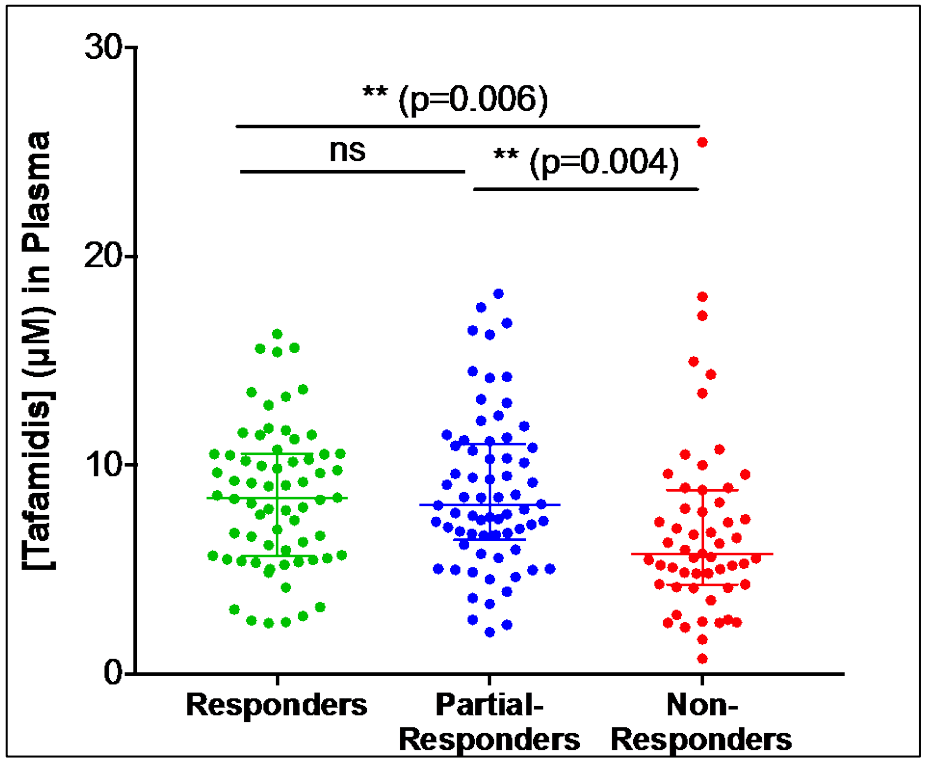
Outcome predictors:

[Tafamidis] Correlates with Outcome

Do we have to increase the dose?



8.7 µM 8.5 µM **6.8 µM**



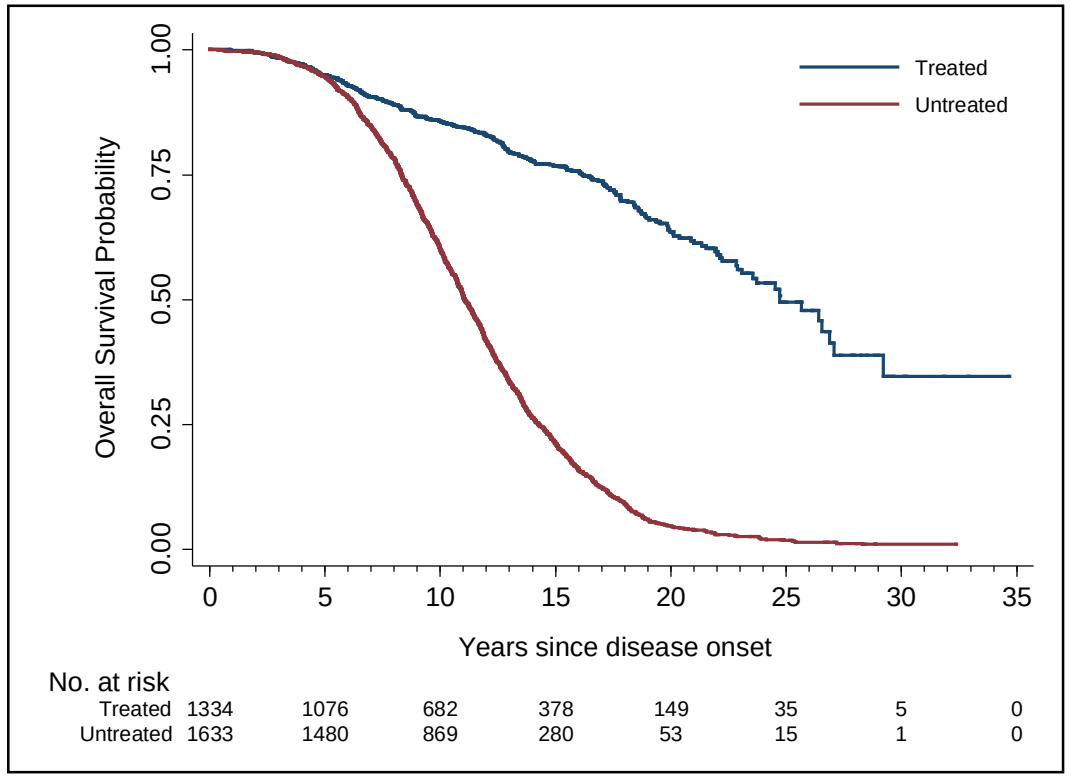
8.5 µM 8.1 µM **5.8 µM**

Liver transplant

Lessons from prolonged survival

Treatment effect on survival in Portuguese patients

TTR-FAP overall treatment can be associated to a 76% reduction in mortality risk compared with natural history: 11 years *vs* 25 years median TTR-FAP survival

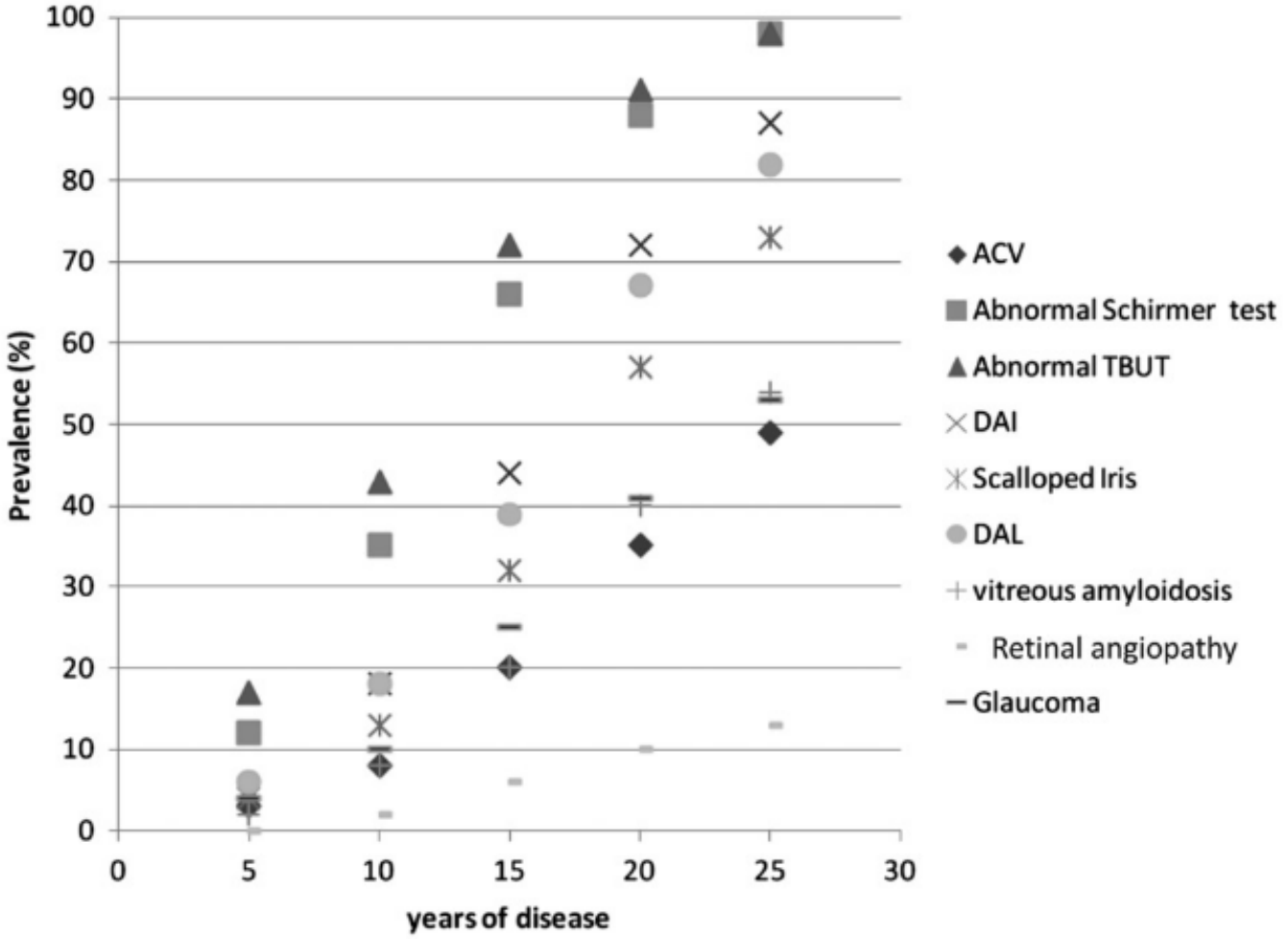


	mOS (years)	95% CI
All Treated	24.73	23.09-27.09
All Untreated	11.05	10.80-11.38

Increased prevalence of eye disease

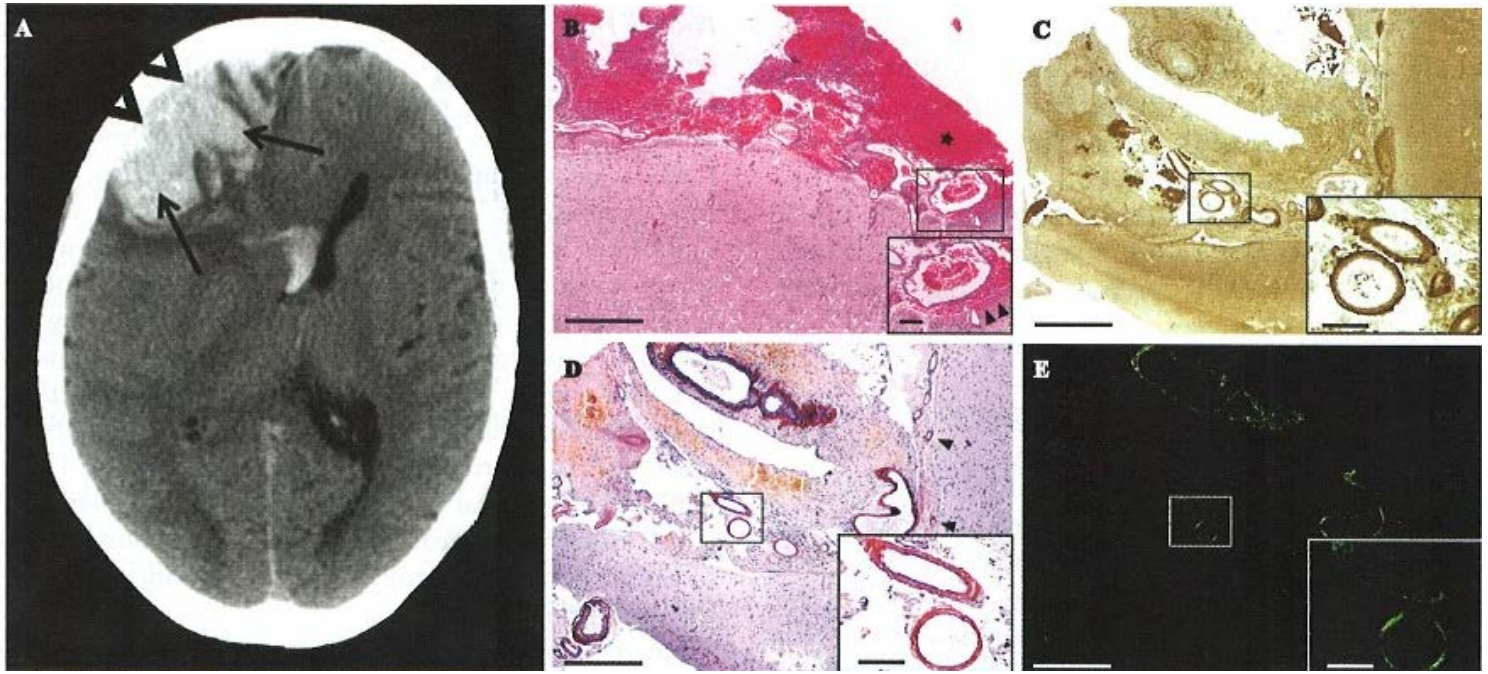
Amyloid, 2015; 22(2): 117–122

Figure 1. Prevalence of each ocular manifestation at 5, 10, 15, 20 and 25 years of disease. All prevalences increased with time. ACV, abnormal conjunctiva vessels; DAI, deposition of amyloid on the iris; DAL, deposition of amyloid on the lens.



Symptoms of CNS involvement are frequently observed

- After eight to ten years patients present focal neurologic signs, mimicking TIAs, focal epileptic seizures and migraine.
- A few cases present dementia
- Some patients have lobar cerebral hemorrhages.

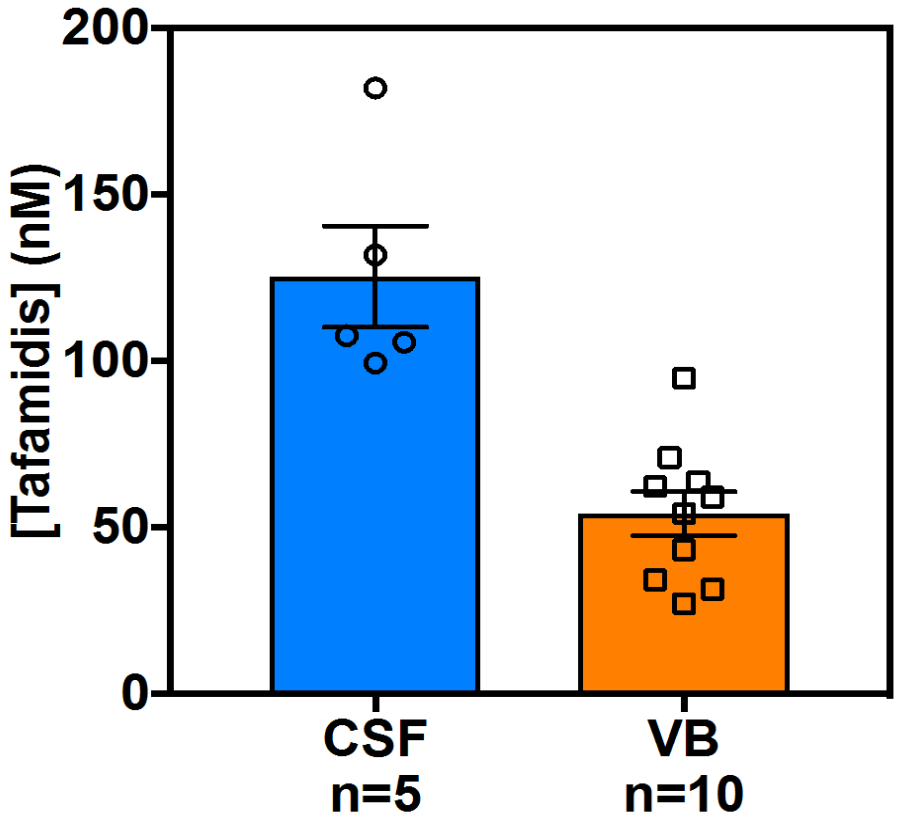


Maia LF, Magalhães R, Freitas J, Taipa R, Pires MM, Osório H, Dias D, Pessegueiro H; Correia M, Coelho T. CNS involvement in V30M transthyretin amyloidosis: clinical, neuropathological and biochemical findings.
J Neurol, Neurosurg and Psychiatry 2015; 86:159-67

Tafamidis

Can it prevent the development of eye and CNS disease?

Tafamidis is detectable and quantifiable in the cerebrospinal fluid (CSF) of 5/5 patients and the vitreous body (VB) of 10/10 patients taking tafamidis orally.



Concentration of Tafamidis in the CSF ranges from 136.2 to 99.4 nM (mean ± s.e.m: 125.3 ± 15.2 nM); in the VB it ranges from 94.8 to 27.1 nM (mean ± s.e.m: 54.2 ± 6.6 nM).

- In the CSF moderate kinetic stabilization of TTR was also found.
- Is this enough to prevent or delay CNS and eye manifestations?
- Could higher oral doses lead to higher [Tafamidis] in the CSF and eye?

Conclusions

- The outstanding results of the two clinical trials with drugs that knock-down TTR open a new era for the treatment of ATTR amyloidosis: the new drugs are efficacious and relatively safe no matter the characteristics of the patients (in what concerns age, genotype, genetic background and disease stage.
- Tafamidis showed efficacy to treat ATTR cardiomyopathy: major doubts remain on the best choice to treat patients with neuropathy and cardiomyopathy
- Tafamidis is able to stabilize the disease in a subset of selected patients and maintains a excellent safety profile in the long term.
- An increased dose may well improve efficacy.
- It has shown potential to enter the eye and CNS and should be evaluated for treatment of these particular expressions of the disease.

Thank you to all patients and families for their resiliance, patience and enthusiasm.

Thank you to all investigators and to all those who contributed to the development of new treatments

Thank you for your attention!