Tafamidis in Transthyretin Amyloid Cardiomyopathy
Effects on Transthyretin Stabilization and Clinical Outcomes

Mathew S. Maurer, MD; Donna R. Grogan, MD; Daniel P. Judge, MD; Rajiv Mundayat, MSc; Jeff Packman, MBA; Iliise Lombardo, MD; Arshed A. Quyyumi, MD; Janske Aarts, MD; Rodney H. Falk, MD

Background—Transthyretin (TTR) amyloidosis is a progressive systemic disorder caused by misfolded TTR monomers that cumulatively deposit in the heart and systemically as amyloid.

Methods and Results—This phase 2 open-label trial evaluated the stabilization of TTR tetramers using 20 mg of tafamidis daily at week 6 (primary end point), month 6, and month 12, as well as safety of tafamidis treatment and efficacy with respect to progression of TTR amyloid cardiomyopathy. Thirty-one wild-type patients (median age, 76.7 years; 93.5% men) with a median disease duration of 55.6 months and mild to moderate heart failure (96.8%; New York Heart Association, classes I–II) were enrolled. Thirty of 31 patients (96.8%) achieved TTR stabilization after 6 weeks and 25 of 28 patients (89.3%) after 12 months. After 12 months of treatment, 3 patients discontinued prematurely, 2 patients died, 7 patients were hospitalized because of cardiovascular events, 20 of 28 patients demonstrated preserved New York Heart Association classification status, but 15 of 31 (48.4%) patients had clinical progression (eg, admission for cardiac failure, atrial fibrillation, and syncope). N-terminal prohormone brain natriuretic peptide levels did not increase significantly over time, troponin I and troponin T increased moderately, and no consistently clinically relevant changes were seen in echocardiographic cardiac assessments. Tafamidis treatment was generally well tolerated although 7 of 31 patients had bouts of diarrhea.

Conclusions—Tafamidis treatment effectively achieved and maintained TTR stabilization and was well tolerated. The absence of significant changes in most biochemical and echocardiographic parameters suggests that further evaluation of tafamidis in TTR amyloid cardiomyopathy is warranted.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00694161.

Key Words: amyloid ■ cardiomyopathies ■ clinical trial ■ heart failure

Transthyretin (TTR) amyloidosis is a heterogeneous disease caused by cumulative, extracellular TTR amyloid deposition that leads to progressive organ dysfunction. TTR, a carrier of retinol and thyroxine, is a homotetrameric plasma protein primarily produced by the liver. Genetic mutations or nonhereditary alteration of TTR protein can destabilize tetramers causing them to dissociate into monomers, leading to monomer misfolding and aggregation into amyloid fibrils. Amyloid fibrils can deposit in various tissues causing a range of clinical manifestations with polynuropathy or cardiomyopathy being the dominant clinical features.

Clinical Perspective on p 526

TTR-associated cardiac amyloidosis is caused by TTR amyloid infiltration of the myocardium and conduction system, which results in a restrictive cardiomyopathy associated with atrial arrhythmias, progressive heart failure, and reduced life expectancy. This underappreciated condition, TTR amyloid cardiomyopathy (TTR-CM), has been associated with aging (senile systemic amyloidosis or wild-type TTR amyloidosis) and with an increasing number of TTR mutations (familial amyloid cardiomyopathy), V122I being the most frequent TTR mutation causing cardiomyopathy. TTR-CM is often misdiagnosed, usually as hypertensive heart disease or hypertrophic cardiomyopathy, and recent studies suggest that it may be more prevalent than previously estimated. Consistent
with previous studies,\textsuperscript{10,11} the Transthyretin Amyloidosis Cardiac Study (TRACS), a prospective cohort study of 29 patients with TTR-CM, demonstrated rapid disease progression, with a median survival from diagnosis of 25.6 months for TRACS patients carrying the V122I TTR mutation and 43.0 months for patients with wild-type disease.\textsuperscript{12,13} Similarly, a recent study in 99 British wild-type TTR-CM patients reported a median survival from diagnosis of 2.71 years (≈35.2 months).\textsuperscript{14} Current treatment for TTR-CM focuses on supportive care, with a minor subset receiving heart transplants.\textsuperscript{14,15}

Tafamidis meglumine (tafamidis; Pfizer Inc, New York, NY) is a novel compound that binds to the thyroxine-binding sites of the TTR tetramer, inhibiting its dissociation into monomers.\textsuperscript{16} By inhibiting tetramer dissociation, tafamidis blocks the rate-limiting step in the TTR amyloid cascade.\textsuperscript{4,17} An 18-month, double-blind, placebo-controlled trial in patients with early stage TTR familial amyloid polyneuropathy (TTR-FAP) because of a TTR V30M mutation demonstrated that tafamidis treatment stabilizes V30M TTR tetramers and slows progression of neurological symptoms that dominate the clinical picture of TTR amyloidosis patients with a V30M mutation.\textsuperscript{18} The present phase 2, multicenter, 12-month trial evaluated the safety of oral tafamidis treatment and effects on TTR stability in patients with wild-type or V122I TTR-CM. Many exploratory efficacy variables were also assessed.

**Methods**

**Study Design**

This open-label, single-treatment arm study was conducted at 6 clinical sites in the United States. After a screening period of \(\frac{4}{4}\) weeks, eligible patients with V122I or wild-type TTR-CM were enrolled and assigned to receive 20 mg of tafamidis once daily (QD). Patients achieving the primary end point of TTR stabilization at week 6 continued tafamidis treatment for 12 months. The study was conducted on an outpatient basis with clinical visits at baseline, weeks 2 and 6, and months 3, 6, and 12. Each patient provided informed consent before engaging in any study procedure.

The study was registered at clinicaltrials.gov (identifier NCT00694161) and conducted in compliance with the International Conference on Harmonization Guidance for Industry on Good Clinical Practice, local country regulations, and ethical principles described in the Declaration of Helsinki (Washington 2002). The complete study protocol was approved by institutional review boards at all study sites. Subsequently, approved amendments to the study protocol clarified monitoring of safety data, increased sample size, allowed identification of amyloid in biopsy specimens by mass spectrometry, and required TTR genotyping during screening for patients without documented diagnosis of TTR-CM. All authors had access to all the data in the study.

**Study Population**

To be eligible, men and postmenopausal women aged \(\geq 40\) years were required to have V122I or wild-type TTR-CM verified by the presence of amyloid in cardiac biopsy tissue, or left ventricular wall thickness of \(\geq 12\) mm (assessed by echocardiography) and presence of amyloid in noncardiac biopsy tissue. The presence of TTR amyloid was determined by Congo red stain, Alcian blue stain plus immunohistochemical TTR analysis, or mass spectrometry. A subset of enrolled patients (V122I: \(n=1\); wild-type: \(n=6\)) had participated in the observational TRACS study.\textsuperscript{16} Optimal management of heart failure symptoms with a stable drug regimen for \(\geq 4\) weeks and, if using a \(\beta\)-blocker, a stable dose for \(\geq 3\) months before enrollment were required. Exclusion criteria included primary or secondary amyloidosis, previous liver or heart transplant, positive results for hepatitis B surface antigen, hepatitis C virus, or HIV, moderate or severe hepatic impairment, abnormal liver function (alanine transaminase and aspartate transaminase >2 \times the upper limit of normal), previous nonamyloid cardiac disease (eg, obstructive coronary artery disease and active nonamyloid cardiomyopathy), or any comorbidity anticipated to limit survival to <12 months. Chronic use of nonsteroidal anti-inflammatory drugs (with the exception of acetaminophen, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac) was prohibited.

**Interventions**

In addition to receiving the standard of care, all enrolled patients were assigned to self-administer an oral capsule containing 20 mg of tafamidis meglumine QD for 12 months. Tafamidis was the only active ingredient in the supplied gel capsules containing 20 mg of tafamidis meglumine (d-glucitol, 1-deoxy-1-[methylamino]-2-[3, 5-dichlorophenyl]-6-benzoxazole carboxylate [1:1]) in suspension. Tafamidis was manufactured by FoldRx Pharmaceuticals (acquired by Pfizer Inc in 2010) in facilities compliant with good manufacturing practices.

**Outcome Measures**

TTR stabilization was determined by a validated immunoturbidimetric assay (performed by Genzyme Analytic Services, Los Angeles, CA).\textsuperscript{19} Briefly, plasma samples were collected and steady-state TTR tetramer stability was determined by comparing TTR tetramer concentration before and after urea denaturation. The ratio of tetramer level postdenaturation to tetramer level predenaturation was termed the fraction of initial (FOI). Percent stabilization was determined by comparing the FOI at each on-drug time point to the FOI at baseline using the following formula:

\[
\text{Percent (\%)}\text{stabilization}=100 \times \left(\frac{\text{FOI}_{\text{on-drug}} - \text{FOI}_{\text{baseline}}}{\text{FOI}_{\text{baseline}}}\right)
\]

The stabilization cut-off value for this study was derived from a phase 1 study in healthy volunteers (Pfizer Inc, data on file). Percent stabilization values falling above the 95\% confidence interval in healthy volunteers were classified as stabilized.

Incidence of mortality and hospitalization was assessed individually and jointly as a composite exploratory end point, where the cause of death or hospitalization was determined by the principal investigator. Analysis of additional exploratory efficacy end points (assessed by echocardiography, chest x-ray, cardiac MRI, and 24-hour Holter monitoring) was conducted at baseline and months 6 and 12. Echocardiography and cardiac MRI were performed using standard techniques, and images were centrally read by blinded core laboratory personnel to ensure consistent interpretation. Functional status of patients with heart failure was assessed using the New York Heart Association classification criteria at baseline, week 6, and months 3, 6, and 12. Cardiac biomarkers (troponin I, troponin T, and N-terminal prohormone brain natriuretic peptide [NT-proBNP]) were monitored at each study visit. Other outcomes included 6-minute walk test (6MWT) and several measures of health-related quality of life: patient global assessment, Kansas City Cardiomyopathy Questionnaire,\textsuperscript{19} and Short Form 36 (SF 36); these were assessed at baseline and months 3, 6, and 12.

**Safety and Tolerability**

Adverse events (AEs), including serious AEs (SAEs), were collected at study visits or by monthly telephone calls. Additional measures of safety included vital signs, physical examinations, 12-lead ECGs, and laboratory assessment of blood and urine samples performed during each clinic visit.

Deaths and SAEs were reviewed bimonthly by an independent data monitoring committee. The data monitoring committee could recommend study termination at any time if they determined that the drug was causing undue harm to patients.
Table 1. Patient Disposition

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Wild-Type, n=31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>31</td>
</tr>
<tr>
<td>Enrolled from TRACS</td>
<td>6 (19.4%)</td>
</tr>
<tr>
<td>Completed study (month 12)</td>
<td>28 (90.3%)</td>
</tr>
<tr>
<td>Received ≥1 dose of tafamidis</td>
<td>31 (100%)</td>
</tr>
<tr>
<td>Prematurely discontinued from the study</td>
<td>3 (9.7%)</td>
</tr>
</tbody>
</table>

Reasons for discontinuation

| AE (glioblastoma multiforme) | 1 (3.2%) |
| AL amyloidosis* | 1 (3.2%) |
| Hemorrhagic stroke* | 1 (3.2%) |

AE indicates adverse event; AL, amyloid light chain; TTR, transthyretin; and TRACS, transthyretin amyloidosis cardiac study.

*Resulted in death during the 12-month study.

Table 2. Demographics and Medical History at Baseline

<table>
<thead>
<tr>
<th>Wild-Type, n=31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (range)</td>
</tr>
<tr>
<td>Sex, male, %</td>
</tr>
<tr>
<td>Race, black/Afro-Caribbean, %</td>
</tr>
<tr>
<td>NYHA classification</td>
</tr>
<tr>
<td>NYHA class I</td>
</tr>
<tr>
<td>NYHA class II</td>
</tr>
<tr>
<td>NYHA class III</td>
</tr>
<tr>
<td>NYHA class IV</td>
</tr>
<tr>
<td>Duration of TTR-CM-related symptoms, mo, median (range)</td>
</tr>
<tr>
<td>Age at TTR-CM symptom onset, years, median (range)</td>
</tr>
<tr>
<td>Potentially clinically significant low hemoglobin levels, %</td>
</tr>
<tr>
<td>Cardiac biomarkers, median (range)</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
</tr>
<tr>
<td>Troponin I, ng/mL</td>
</tr>
<tr>
<td>Troponin T, ng/mL</td>
</tr>
<tr>
<td>Atrial fibrillation,* n (%)</td>
</tr>
<tr>
<td>Heart block,† n (%)</td>
</tr>
<tr>
<td>Carpal tunnel syndrome, n (%)</td>
</tr>
<tr>
<td>Cardiac pacemaker/implantable defibrillator insertion, n (%)</td>
</tr>
</tbody>
</table>

NT-proBNP indicates N-terminal prohormone brain natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin; and TTR-CM, transthyretin-cardiomyopathy.

*These numbers include patients with a history of atrial fibrillation that had resolved at the time of study entry.
†Heart blocks included atrioventricular block of first degree, bifascicular block, left bundle branch block, and right bundle branch block.
TTR Stabilization (Primary End Point)
Tafamidis effectively stabilized TTR in 30 of 31 patients (96.8%) at week 6 (Table 3). The only patient lacking stabilization did not have any safety concerns and remained in the study after careful review by the principal investigator and notification of the internal review board. TTR stabilization was not achieved for this patient throughout the study, and the clinical course of the patient was similar to that of the overall population. TTR stabilization was observed in 27 of 30 patients (90.0%) at month 6 and in 25 of 28 (89.3%) at month 12.

Safety
Death or Cardiovascular Hospitalization
Two patients died during the study period: 1 patient originally classified as wild-type TTR-CM died from complications resulting from AL amyloidosis, as discussed above. The other died on study day 105 of a hemorrhagic stroke occurring after a fall.

During 12 months of tafamidis treatment, 7 patients (22.6%) were hospitalized because of cardiovascular events. Two of these had 1 cardiovascular hospitalization each, and 5 had 2 cardiovascular hospitalizations each. Six of the 12 cardiovascular hospitalizations were assessed to be related to heart failure.

Serious Adverse Events
SAEs were experienced by 13 of 31 patients (41.9%; Table 4). Most were cardiac events, such as worsening heart failure (8 patients, 25.8%) and atrial fibrillation (3 patients, 9.7%). In addition, 2 patients had an SAE categorized as syncope and 1 of these had a pacemaker implanted. One additional patient had an SAE categorized as pacemaker insertion. Four patients experienced SAEs that were assessed as possibly related to tafamidis. These included ataxia, falls, heart failure, a fall-induced hemorrhagic stroke, and syncope. With the exception of the 2 deaths, all patients with an SAE had recovered or were improving by the study end.

Adverse Events
Reflecting the study populations’ underlying cardiac disease, elderly status, and comorbid conditions, all 31 patients experienced ≥1 AE during the study (Data Supplement). The most frequent AEs were symptoms or episodes of heart failure, such as dyspnea, worsening heart failure, and edema. Seven of 31 patients (22.6%) had an AE of diarrhea (including 2 enrolled as dyspnea, worsening heart failure, and edema). Seven of 31 patients (22.6%) were experiencing heart failure, including 2 enrolled as dyspnea, worsening heart failure, and edema.

In addition, 2 patients had an SAE categorized as syncope and 1 of these had a pacemaker implanted. One additional patient had an SAE categorized as pacemaker insertion. Four patients experienced SAEs that were assessed as possibly related to tafamidis. These included ataxia, falls, heart failure, a fall-induced hemorrhagic stroke, and syncope. With the exception of the 2 deaths, all patients with an SAE had recovered or were improving by the study end.

Summary of Adverse Events
Table 4. Summary of Adverse Events

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Wild-Type, n=31</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of AEs</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with ≥2 AE</td>
<td>n=31 (100)</td>
</tr>
<tr>
<td>No. of patients with ≥2 SAE</td>
<td>13 (41.9)</td>
</tr>
<tr>
<td>Patients who discontinued because of an AE</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>8 (25.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Fall</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Syncope</td>
<td>2 (6.5)</td>
</tr>
</tbody>
</table>

AE indicates adverse event; and SAE, serious adverse event.

*Primary end point.
†Only those SAEs occurring in ≥2 patients are listed. Any patient with multiple incidences is counted only once per category.

Cardiac Assessments
Echocardiogram assessment demonstrated extensive cardiac involvement in all patients with a baseline assessment (n=30; Table 5). All patients (100%) demonstrated markedly increased left ventricular wall thickness (interventricular septum and left ventricular posterior wall). Elevation of left ventricular (high E/E’ septal ratio) and right ventricular (absent vena cava respiratory variations) cardiac filling pressures was seen in 73.7% and 64.0% of patients, respectively; 43.3% had an ejection fraction of <50%. There were no consistent clinically relevant changes in these echocardiogram parameters during 12 months of tafamidis treatment. As a result of the high prevalence of patients with pacemakers (n=15; 13 before and 2 during the study), only a limited subset of patients underwent cardiac MRI (Data Supplement).

Nearly all patients had electrocardiographic (100%) and Holter monitoring (80.0%) abnormalities at enrollment. The most common pretreatment ECG abnormalities were abnormal conduction (90.3%), abnormal rhythm (67.7%), pathologic Q waves (19.4%), and abnormal T wave (19.4%). The incidence of treatment-emergent ECG abnormalities was low, with no adverse effect of tafamidis on rhythm or conduction. Holter monitoring abnormalities detected at baseline were indicative of intermittent dysrhythmias and included nonsustained ventricular tachycardia (56.7%), atrial tachycardia (36.7%), atrial fibrillation/flutter (20.0%), and sinus pause (6.7%; Table 6). Consistent with a study population with advanced cardiac disease, treatment-emergent new onset atrial fibrillation/flutter was reported in 8 of 18, nonsustained ventricular tachycardia in 4 of 11, and sinus pause in 5 of 24 patients at month 12.

At baseline, the median NT-proBNP concentration was elevated (3178 pg/mL; range, 719–18,401 pg/mL; normal upper limit, 300 pg/mL), and all but 1 patient had values indicative of a high probability of heart failure (≥1000 pg/mL).21 There was large variation in NT-proBNP concentrations and changes in nearly all patients after 1 year of treatment; a decrease was seen in 11 patients (35.4%), no change in 12 patients (38.7%), and an increase in 8 patients (25.9%).
Maurer et al. Tafamidis in TTR Cardiomyopathy

therein between patients with a nonsignificant estimated LS mean (±SE) increase from baseline to month 12 of 601 (±926) pg/mL (Figure 1). The baseline concentration of troponin I was raised in 100% of patients (median, 0.120 ng/mL; range, 0.06–0.41 ng/mL; normal upper limit, 0.04 ng/mL). After an initial decrease from baseline to month 3, there was an increase in troponin I (LS mean [±SE] change from baseline to month 12, 0.037 [±0.020] ng/mL; $P<0.05$). Troponin T concentrations were raised in 93.5% of patients at baseline (median, 0.030 ng/mL; range, 0.010–0.160 ng/mL; normal upper limit, 0.01 ng/mL), remained stable during the first 3 months of tafamidis treatment, and were higher relative to baseline at month 6 (LS mean [±SE] change, 0.010 [±0.006] ng/mL; $P<0.05$) and month 12 (LS mean [±SE] change, 0.005 [±0.006] ng/mL; $P>0.05$).

### Functional and Quality of Life Assessments

Change in functional walking ability, measured by the 6MWT, was minimal. The mean distance walked decreased by 8.9 meters from baseline to month 12. Categorical analysis confirmed that most patients maintained their walking status (Figure 2). New York Heart Association classification was maintained in 71.4% patients at month 12 and no patient deteriorated by ≥2 classes or dropped to New York Heart Association classification IV. Overall, patients reported preserved

### Table 5. Echocardiographic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline*</th>
<th>Change From Baseline at Month 12†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventricular septum thickness, mm</td>
<td>n=30</td>
<td>n=27</td>
</tr>
<tr>
<td>Left ventricle posterior wall thickness, mm</td>
<td>n=30</td>
<td>n=27</td>
</tr>
<tr>
<td>Right ventricle wall thickness, mm</td>
<td>n=24</td>
<td>n=19</td>
</tr>
<tr>
<td>Left atrial diameter, anterior-posterior, mm</td>
<td>n=30</td>
<td>n=27</td>
</tr>
<tr>
<td>Left ventricle ejection fraction, %</td>
<td>n=30</td>
<td>n=27</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>n=21</td>
<td>n=18</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>n=29</td>
<td>n=26</td>
</tr>
<tr>
<td>Tricuspid PASP,‡ mm Hg</td>
<td>n=27</td>
<td>n=22</td>
</tr>
<tr>
<td>E/E’ lateral ratio</td>
<td>n=22</td>
<td>n=12</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>n=16</td>
<td>n=7</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>n=19</td>
<td>n=14</td>
</tr>
</tbody>
</table>

### Table 6. Holter Monitoring Abnormalities

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline†</th>
<th>Month 12‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any abnormality</td>
<td>24/30 (80.0)</td>
<td>14/26 (53.8)</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>6/30 (20.0)</td>
<td>8/18 (44.4)</td>
</tr>
<tr>
<td>Atrial tachycardia</td>
<td>11/30 (36.7)</td>
<td>0/16 (0.0)</td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia (&lt;30 beats)</td>
<td>17/30 (56.7)</td>
<td>4/11 (36.4)</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia (≥30 beats)</td>
<td>0/30 (0.0)</td>
<td>1/26 (3.8)</td>
</tr>
<tr>
<td>Sinus pause</td>
<td>2/30 (6.7)</td>
<td>5/24 (20.8)</td>
</tr>
</tbody>
</table>

*Number with abnormality/number eligible for assessment (%) at visit. †One patient had no Holter monitoring test at baseline. ‡Ratios exclude those patients with abnormal values at baseline and give the frequency of treatment-emergent abnormalities.

Figure 1. Least square (LS) mean change from baseline in N-terminal prohormone brain natriuretic peptide (NT-proBNP: A), troponin I (B), and troponin T (C) during tafamidis treatment. Median (range) baseline concentrations were 3178.0 (719–18401) pg/mL, 0.12 (0.06–0.41) ng/mL, and 0.03 (0.01–0.16) ng/mL, respectively. Error bars represent SE. Asterisks indicate statistically significant changes from baseline to the given time point (2-sided $P<0.05$).
health-related quality of life during the study: the majority of patients (range, 71.4–86.7%) rated their disease status as unchanged or improved (patient global assessment, Figure 3) and changes in Kansas City Cardiomyopathy Questionnaire and Short Form 36 scores were minor (Data Supplement).

Clinical Disease Progression

Although clinical indicators of disease progression and treatment response have been delineated in AL amyloidosis,22 such data are lacking in TTR-CM. In the absence of prospective clearly defined criteria, we operationalized a definition of clinical disease stability in which patients who died, had a hospitalization for a cardiac event, a rise in NT-proBNP of >1000 pg/mL, an increase in serum creatinine of ≥0.5 mg/dL, or a >50-m decline in distance walked in the 6MWT were considered to have progressed during a 12-month period. On the basis of this non-validated definition, 15 of 31 patients progressed while taking 20 mg of tafamidis for 12 months.

Discussion

This phase 2 open-label study demonstrates that tafamidis treatment was effective in achieving and maintaining TTR stabilization in patients with TTR-CM. AEs reported during the study are in line with expectations for an elderly population with significant heart disease and suggest that tafamidis is well tolerated in patients with TTR-CM. Despite small but statistically significant increases in troponin I and T relative to baseline levels, the absence of clinically significant changes in most clinical, biochemical, electrocardiographic, and echocardiographic parameters is consistent with the potential for tafamidis to slow cardiac disease progression.

TTR-stabilizing compounds, such as tafamidis or difluoromethylornithine,23 are expected to limit the progression of TTR amyloidosis by inhibiting tetramer dissociation, the rate-limiting step in TTR amyloid formation. In a randomized, double-blind trial of tafamidis in TTR-FAP patients with a V30M mutation, TTR stabilization was demonstrated in 98% of patients receiving tafamidis and in none of the control subjects (P<0.001) during the 18-month trial.21 Patients receiving tafamidis experienced significantly less deterioration in neurological and functional status as indexed by Neuropathy Impairment Score for the Lower limbs (NIS-LL; P=−0.041) and the Norfolk total quality of life scores (TQoL; P=0.045) in the efficacy evaluable population. Two recent single-arm, open-label studies reported that tafamidis stabilizes tetrameric TTR also in TTR-FAP patients with non-V30M and non-V122I mutations,24 but that it may be less efficient in preventing disease progression in V30M patients with advanced disease.25 On the basis of common mechanism of disease, we hypothesized that, like in early stage TTR-FAP, tafamidis might also stabilize TTR tetramers and slow disease progression in patients with TTR-CM.

TTR-stabilizing agents are designed to prevent de novo deposition of TTR amyloid by blocking the rate-limiting step in the TTR amyloid cascade, and because the pathogenesis of all types of TTR amyloidosis is believed to be related to increased tetramer dissociation, TTR tetramer stabilization is a critical first step in demonstrating the potential for tafamidis to slow cardiac disease progression. However, they are not necessarily expected to actively induce the reabsorption of existing amyloid deposits. An alternative approach is TTR gene silencing, which is being evaluated in 2 prospective ongoing clinical trials of antisense oligonucleotides and small interfering RNA in TTR-FAP26,27 and a phase 2 study to evaluate RNA interference therapy in patients with TTR cardiac amyloidosis (clinicaltrials.gov identifier: NCT01981837).

The safety and efficacy of such an approach are currently unknown. Whether these agents will be comparable, superior, or inferior to TTR stabilization and whether combination therapy will afford clinical benefit are likely to be a focus of ongoing investigation.
Although the immunoturbidity assay is well suited to demonstrate TTR stabilization in the vast majority of patients, by definition, a high FOI at baseline necessitates a proportionally larger increase in postdose FOIs to be considered stabilized. Indeed, 4 of the 5 patients who did not achieve consistent TTR stabilization in this study had baseline FOIs of >0.4, range 0.42 to 0.60. In contrast, 29 of 30 patients who were stabilized at every assessment had baseline FOIs of <0.35, range 0.15 to 0.34. It remains to be determined whether a high baseline FOI equates with a higher TTR tetramer stability under physiological conditions that may not be further increased by tafamidis. Another inherent limitation of this assay conducted under nonphysiological conditions is that it was developed as a qualitative assessment of TTR stabilization and not a quantitative measure of the degree of stabilization. Despite these limitations, the assay is an appropriate primary end point for this hypothesis-generating, open-label trial, especially as increases in TTR stability after administration of tafamidis are unlikely to be the result of placebo effects or of natural improvements over time but are highly likely to be treatment-related.

The single-arm design of this study limits the ability to demonstrate efficacy of tafamidis on outcome measures. TTR-CM is a progressive disorder. Published series to date have reported 1-year mortality of 14% to 23% in wild-type TTR-CM subjects.11,12,28 Serial measurements of clinical parameters used in this interventional study were also used in the observational, prospective TRACS study that examined the natural history of 18 untreated wild-type and 11 V122I TTR-CM patients. In the absence of a parallel control cohort, comparison of observed event rates to those observed in TRACS may allow for the safety and exploratory results to be put into context.12 After 12 months of follow-up, 2 of 18 wild-type TTR-CM patients enrolled in TRACS (11.1%) died and 3 (16.7%) were hospitalized because of cardiovascular events. Looking at median (range) change from baseline to month 12, the NT-proBNP concentration increased by 1487 (–2331 to 4958) pg/mL to 6268 (1206 to 9506) pg/mL; the distance walked in the 6MWT increased by 0.6 (–206 to 39.3) m to 359.5 (166.0 to 665.0) m, and left ventricular ejection fraction monitored by echocardiography decreased by –8.0% (–39.0% to 1.0%) to 50.5% (25.0% to 67.0%). Increases from baseline to month 12 in troponin I (median, 0.02 ng/mL; range, –0.03–0.07 ng/mL; n=8) and troponin T (median, 0.01 ng/mL, range, –0.01–0.09 ng/mL, n=4) observed in TRACS did not markedly exceed those observed in this study. However, in the absence of a parallel control group, it cannot be determined with certainty whether increases in troponin I and T concentrations would have been more pronounced in the absence of tafamidis in the current population. With regard to clinical progression, 15 of 31 (48.4%) of wild-type patients who received 20 mg of tafamidis progressed as defined by either death, cardiovascular hospitalization, a rise in NT-proBNP of >1000 pg/mL, an increase in serum creatinine of ≥0.5 mg/dL, or a decline in the distance walked in the 6MWT of >50 m during the 12-month study period, whereas 21 of 29 (72.4%) of wild-type subjects progressed during the first 12 months of the TRACS study. Whether a higher dose of tafamidis (eg, 80 mg) will be more effective is currently being evaluated in the ongoing clinical trial assessing the safety and tolerability of an oral dose of 20 mg or 80 mg of tafamidis meglumine in patients with TTR-CM (clinicaltrials.gov identifier NCT01994889).

This trial was also limited by the relatively small patient numbers. The clinical identification of patients with TTR-CM and their enrollment into clinical studies is restricted by the heterogeneity of symptoms, many of which are nonspecific disease manifestations commonly seen in older persons; by low awareness of the condition; and the ensuing high frequency of misdiagnosis.29 As a result of the low number of patients enrolled and the relatively small number who did not achieve TTR stabilization, whether TTR-CM patients who fail to achieve consistent TTR stabilization experience more severe disease progression is not known but will be evaluated in larger trials.

In conclusion, this study provides evidence that tafamidis treatment resulted in TTR stabilization in patients with TTR-CM. Consequently, further study of tafamidis in the TTR-CM amyloidosis population is warranted to determine whether TTR-CM disease progression can be modified by this TTR tetramer stabilization treatment.

Acknowledgments

We thank Savitri Fedson, MD, University of Chicago, Chicago, IL, as well as Steven Zeldenrust, MD, Mayo Clinic College School of Medicine, Rochester, MN, for their contributions to study supervision, and data collection, analysis, and interpretation. Medical writing support was provided by John Clinton Earnheart, PhD, from Scientific Strategy Partners and by Susanne Vidot, PhD, from Engage Scientific Solutions and funded by Pfizer.

Sources of Funding

This study was sponsored by FoldRx Pharmaceuticals Inc, which was acquired by Pfizer in October 2010.

Disclosures

Dr Maurer has received support from FoldRx Pharmaceuticals, which was acquired by Pfizer in October 2010, as a clinical investigator and for scientific meeting expenses. His institution has received grant support from Pfizer. Dr Grogan and J. Packman were employees of FoldRx Pharmaceuticals, which was acquired by Pfizer in 2010, during the conduct of this trial and preparation of the article. Drs Judge and Falk have received funding from FoldRx Pharmaceuticals, which was acquired by Pfizer in October 2010, as consultants and clinical investigators and from Pfizer as consultants. R. Mundayat and Dr Aarts are employees of Pfizer. Dr Lombardo was an employee of Pfizer during the conduct of this trial and preparation of the article.

References

6. Ravezzi C, Quarta CC, Riva L, Longhi S, Gallelli I, Lorenzini M, Ciliberti P, Biagini E, Salvi F, Branzi A. Transthyretin-related amyloidoses and...
Transthyretin amyloidosis is a fatal systemic disorder caused by misfolded transthyretin monomers aggregating into amyloid fibrils that progressively accumulate in the heart and other tissues. Tafamidis is a first-in-class transthyretin stabilizer designed to prevent transthyretin tetramer dissociation, the rate-limiting step of the transthyretin-related amyloidogenic process. This article describes the first clinical evaluation of tafamidis in patients with a virtually exclusive cardiac phenotype characterized by cardiomyopathy and congestive heart failure. We report that treatment with 20 mg of tafamidis daily in an open-label, single-arm study with 35 participants was well tolerated and effectively stabilized tetrmeric transthyretin protein (primary efficacy endpoint). The prospect of a medical therapy targeting the underlying biology of this condition will help encourage practicing clinicians involved in the management of heart failure to consider transthyretin amyloid cardiomyopathy in their differential diagnoses. Such a shift will allow the initiation of appropriate treatment and facilitate the determination of the real prevalence of Val122Ile and wild-type transthyretin-related cardiac amyloidosis, often thought to be overlooked and underappreciated.
Tafamidis in Transthyretin Amyloid Cardiomyopathy: Effects on Transthyretin Stabilization and Clinical Outcomes

Mathew S. Maurer, Donna R. Grogan, Daniel P. Judge, Rajiv Mundayat, Jeff Packman, Ilise Lombardo, Arshed A. Quyyumi, Janske Aarts and Rodney H. Falk

_Circ Heart Fail._ 2015;8:519-526; originally published online April 14, 2015;
doi: 10.1161/CIRCHEARTFAILURE.113.000890
_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/8/3/519

Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2015/04/14/CIRCHEARTFAILURE.113.000890.DC1
http://circheartfailure.ahajournals.org/content/suppl/2016/12/26/CIRCHEARTFAILURE.113.000890.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Heart Failure_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Heart Failure_ is online at:
http://circheartfailure.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL

Tafamidis in Transthyretin Amyloid Cardiomyopathy: Effects on Transthyretin Stabilization and Clinical Outcomes

Mathew S. Maurer, MD; Donna R. Grogan, MD; Daniel P. Judge, MD; Rajiv Mundayat, MSc; Jeff Packman, MBA; Ilise Lombardo, MD; Arshed A. Quyyumi, MD; Janske Aarts, MD; Rodney H. Falk, MD
Index

1. **Additional Outcome and Safety Results for the ITT Population**

   Supplemental Table 1.1. Patient Disposition by TTR Genotype 3
   Supplemental Table 1.2. Demographics and Medical History at Baseline by TTR Genotype 4
   Supplemental Table 1.3. TTR Stabilization by TTR Genotype 5
   Supplemental Table 1.4. Summary of Adverse Events by TTR Genotype 6
   Supplemental Table 1.5. Echocardiographic Parameters by TTR Genotype 7
   Supplemental Table 1.6. Holter Monitoring Abnormalities by TTR Genotype 8
   Supplemental Table 1.7. Cardiac magnetic resonance imaging results in the Overall ITT population 9
   Supplemental Figure 1.1. Cardiac biomarker concentrations in the V122I Subpopulation 10
   Supplemental Figure 1.2. 6-minute walk test results in the overall ITT population and the V122I subpopulation 11
   Supplemental Figure 1.3. Patient global assessment results in the overall ITT population and the V122I subpopulation 12
   Supplemental Figure 1.4. Results of the Kansas City Cardiomyopathy Questionnaire and Short Form 36 Quality of Life Questionnaire in the WT and V122I subpopulations 13

2. **Efficacy outcome results excluding data of the AL amyloidosis patient erroneously diagnosed with wild-type TTR-CM at study entry.**

   Supplemental Method 2.1. Narrative of diagnosis of AL amyloidosis patient 14
   Supplemental Table 2.1. TTR stabilization results excluding data of the AL amyloidosis patient 15
   Supplemental Table 2.2. Echocardiographic results excluding data of the AL amyloidosis patient 16
   Supplemental Table 2.3. Holter monitoring results excluding data of the AL amyloidosis patient 17
   Supplemental Figure 2.1. Cardiac biomarker concentrations excluding data of the AL amyloidosis patient 18
   Supplementary Figure 2.2. Results of 6-minute walk test excluding data of the AL amyloidosis patient 19
   Supplemental Figure 2.3. Results of patient global assessment excluding data of the AL amyloidosis patient 20
## 1. Additional Safety and Outcome Data for the ITT Population

### Supplemental Table 1.1. Patient Disposition by TTR Genotype

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Overall N=35</th>
<th>V122I N=4</th>
<th>Wild-Type N=31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>35</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>Enrolled from TRACS</td>
<td>7 (20%)</td>
<td>1 (25%)</td>
<td>6 (19.4%)</td>
</tr>
<tr>
<td>Completed study (Month 12)</td>
<td>32 (91.4%)</td>
<td>4 (100%)</td>
<td>28 (90.3%)</td>
</tr>
<tr>
<td>Received ≥1 dose of study drug</td>
<td>35 (100%)</td>
<td>4 (100%)</td>
<td>31 (100%)</td>
</tr>
<tr>
<td>Prematurely discontinued from study</td>
<td>3 (8.6%)</td>
<td>0</td>
<td>3 (9.7%)</td>
</tr>
<tr>
<td>Reasons for discontinuation:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE (glioblastoma multiforme)</td>
<td>1 (2.9%)</td>
<td>0</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>AL amyloidosis*</td>
<td>1 (2.9%)</td>
<td>0</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>Hemorrhagic stroke*</td>
<td>1 (2.9%)</td>
<td>0</td>
<td>1 (3.2%)</td>
</tr>
</tbody>
</table>

TTR indicates transthyretin; TRACS, Transthyretin Amyloidosis Cardiac Study; and AE, adverse event.

*Resulted in death during the 12-month study.
Supplemental Table 1.2. Demographics and Medical History at Baseline by TTR Genotype

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>V122I</th>
<th>Wild-Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=35</td>
<td>N=4</td>
<td>N=31</td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>76.3 (68.1 to 86.5)</td>
<td>73.4 (68.1 to 76.2)</td>
<td>76.7 (68.7 to 86.5)</td>
</tr>
<tr>
<td>Gender, % male, n (%)</td>
<td>32 (91.4)</td>
<td>3 (75.0)</td>
<td>29 (93.5)</td>
</tr>
<tr>
<td>Race, % African-American/Afro-Caribbean</td>
<td>4 (11.4)</td>
<td>4 (100.0)</td>
<td>0</td>
</tr>
<tr>
<td>NYHA classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA Class I</td>
<td>5 (14.3)</td>
<td>0</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>28 (80.0)</td>
<td>3 (75.0)</td>
<td>25 (80.6)</td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>2 (5.7)</td>
<td>1 (25.0)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>NYHA Class IV</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Duration of TTR-CM-related symptoms, months, median (range)</td>
<td>59.6 (6.4 to 348.9)</td>
<td>71.5 (37.2 to 117.9)</td>
<td>55.6 (6.4 to 348.9)</td>
</tr>
<tr>
<td>Age at TTR-CM symptom onset, years, median (range)</td>
<td>73.0 (62.0 to 85.0)</td>
<td>69.5 (66.0 to 72.0)</td>
<td>74.0 (62.0 to 85.0)</td>
</tr>
<tr>
<td>Potentially clinically significant low hemoglobin levels, n (%)</td>
<td>1 (2.9)</td>
<td>0</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Cardiac biomarkers, median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>3224 (719 to 18401)</td>
<td>5318 (5075 to 5560)</td>
<td>3178 (719 to 18401)</td>
</tr>
<tr>
<td>Troponin I, ng/mL</td>
<td>0.13 (0.06 to 0.41)</td>
<td>0.14 (0.14 to 0.14)</td>
<td>0.12 (0.06 to 0.41)</td>
</tr>
<tr>
<td>Troponin T, ng/mL</td>
<td>0.03 (0.01 to 0.16)</td>
<td>0.07 (0.05 to 0.08)</td>
<td>0.03 (0.01 to 0.16)</td>
</tr>
<tr>
<td>Atrial fibrillation*, n (%)</td>
<td>21 (60.0)</td>
<td>1 (25.0)</td>
<td>20 (64.5)</td>
</tr>
<tr>
<td>Heart block†, n (%)</td>
<td>11 (31.4)</td>
<td>0</td>
<td>11 (35.5)</td>
</tr>
<tr>
<td>Carpal tunnel syndrome, n (%)</td>
<td>9 (25.7)</td>
<td>1 (25.0)</td>
<td>8 (25.8)</td>
</tr>
<tr>
<td>Cardiac pacemaker/Implantable defibrillator insertion, n (%)</td>
<td>14 (40.0)</td>
<td>1 (25.0)</td>
<td>13 (41.9)</td>
</tr>
</tbody>
</table>

TTR indicates transthyretin; TTR-CM, transthyretin-cardiomyopathy; and NYHA, New York Heart Association.

*These numbers include patients with a prior history of atrial fibrillation that had resolved at the time of study entry.

†Heart blocks included atrioventricular block of first degree, bifascicular block, left bundle branch block, and right bundle branch block.
### Supplemental Table 1.3. TTR Stabilization by TTR Genotype

<table>
<thead>
<tr>
<th>Visit</th>
<th>Patients evaluated, n</th>
<th>Patients stabilized, n (%)</th>
<th>95% CI</th>
<th>TTR Genotype</th>
<th>Overall N=35</th>
<th>V122I N=4</th>
<th>Wild-Type N=31</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 6</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>34 (97.1)</td>
<td>85.1–99.9</td>
<td></td>
<td>4</td>
<td>4 (100)</td>
<td>30 (96.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Month 6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>30 (88.2)</td>
<td>72.5–96.7</td>
<td></td>
<td>4</td>
<td>3 (75.0)</td>
<td>27 (90.0)</td>
</tr>
<tr>
<td><strong>Month 12</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>28 (87.5)</td>
<td>71.0–96.5</td>
<td></td>
<td>4</td>
<td>3 (75.0)</td>
<td>25 (89.3)</td>
</tr>
</tbody>
</table>

TTR indicates transthyretin; and CI, confidence interval.

*Primary end point.
### Supplemental Table 1.4. Summary of Adverse Events by TTR Genotype

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Overall N=35</th>
<th>V122I N=4</th>
<th>Wild-Type N=31</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of AEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with $\geq$1 AE</td>
<td>35 (100)</td>
<td>4 (100)</td>
<td>31 (100)</td>
</tr>
<tr>
<td>Number of patients with $\geq$1 SAE</td>
<td>15 (42.9)</td>
<td>2 (50.0)</td>
<td>13 (41.9)</td>
</tr>
<tr>
<td>Patients who discontinued due to an AE</td>
<td>1 (2.9)</td>
<td>0</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td><strong>Most common AEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11 (31.4)</td>
<td>1 (25.0)</td>
<td>10 (32.3)</td>
</tr>
<tr>
<td>Dyspnea exertional</td>
<td>6 (17.1)</td>
<td>0</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>Cardiac failure congestive</td>
<td>9 (25.7)</td>
<td>2 (50.0)</td>
<td>7 (22.6)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>4 (11.4)</td>
<td>1 (25.0)</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (20.0)</td>
<td>0</td>
<td>7 (22.6)</td>
</tr>
<tr>
<td>Dizziness postural</td>
<td>6 (17.1)</td>
<td>0</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (22.9)</td>
<td>0</td>
<td>8 (25.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (20.0)</td>
<td>0</td>
<td>7 (22.6)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (17.1)</td>
<td>0</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6 (17.1)</td>
<td>1 (25.0)</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>6 (17.1)</td>
<td>0</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>Edema</td>
<td>3 (8.6)</td>
<td>0</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>6 (17.1)</td>
<td>0</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>Weight increased</td>
<td>5 (14.3)</td>
<td>0</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>5 (14.3)</td>
<td>0</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (14.3)</td>
<td>1 (25.0)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (14.3)</td>
<td>1 (25.0)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>4 (11.4)</td>
<td>0</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Ageusia</td>
<td>3 (8.6)</td>
<td>0</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3 (8.6)</td>
<td>1 (25.0)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>3 (8.6)</td>
<td>0</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>3 (8.6)</td>
<td>0</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3 (8.6)</td>
<td>0</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3 (8.6)</td>
<td>1 (25.0)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3 (8.6)</td>
<td>0</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Thirst</td>
<td>3 (8.6)</td>
<td>0</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (8.6)</td>
<td>0</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3 (8.6)</td>
<td>1 (25.0)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Fall</td>
<td>3 (8.6)</td>
<td>0</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (8.6)</td>
<td>1 (25.0)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (8.6)</td>
<td>1 (25.0)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Skin ulcer</td>
<td>3 (8.6)</td>
<td>0</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (8.6)</td>
<td>1 (25.0)</td>
<td>2 (6.6)</td>
</tr>
<tr>
<td>Seasonal allergy</td>
<td>3 (8.6)</td>
<td>0</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>10 (28.6)</td>
<td>2 (50.0)</td>
<td>8 (25.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (8.6)</td>
<td>0</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Fall</td>
<td>3 (8.6)</td>
<td>0</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Syncope</td>
<td>2 (5.7)</td>
<td>0</td>
<td>2 (6.5)</td>
</tr>
</tbody>
</table>

*Only those AEs occurring in $>$2 patients in overall study population are listed. Any patient with multiple incidences is counted only once per category.

†Only those SAEs occurring in $\geq$2 patients are listed. Any patient with multiple incidences is counted only once per category.
<table>
<thead>
<tr>
<th>Parameter, median (range)</th>
<th>N=35</th>
<th>Overall</th>
<th>TTR Genotype</th>
<th>Wild-Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>V122I N=4</td>
<td>Wild-Type N=31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interventricular septum thickness (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=34</td>
<td>20.0 (14 to 31)</td>
<td>n=4</td>
<td>20.0 (14 to 31)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0 (-8 to 4)</td>
<td>n=3</td>
<td>1.0 (-8 to 4)</td>
</tr>
<tr>
<td>LV posterior wall thickness (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=34</td>
<td>20.0 (14 to 28)</td>
<td>n=4</td>
<td>19.5 (16 to 23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0 (-5 to 3)</td>
<td>n=3</td>
<td>-2.0 (-3 to 3)</td>
</tr>
<tr>
<td>Right ventricle wall thickness (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=27</td>
<td>10.0 (4 to 14)</td>
<td>n=2</td>
<td>11.0 (7 to 11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0 (-4 to 5)</td>
<td>n=3</td>
<td>3.0 (3 to 3)</td>
</tr>
<tr>
<td>Left atrial diameter, anterior-posterior (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=34</td>
<td>44.0 (33 to 60)</td>
<td>n=4</td>
<td>43.0 (39 to 48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0 (-10 to 9)</td>
<td>n=3</td>
<td>-2.0 (-7 to 1)</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=34</td>
<td>50.0 (17 to 70)</td>
<td>n=4</td>
<td>44.0 (17 to 51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-4.0 (-29 to 20)</td>
<td>n=3</td>
<td>6.0 (-6 to 8)</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=25</td>
<td>37.0 (17 to 51)</td>
<td>n=4</td>
<td>24.0 (19 to 29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1.0 (-19 to 13)</td>
<td>n=3</td>
<td>-1.0 (-8 to 2)</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=33</td>
<td>24.0 (2 to 43)</td>
<td>n=4</td>
<td>22.5 (10 to 29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1.0 (-17 to 10)</td>
<td>n=4</td>
<td>5.0 (0 to 5)</td>
</tr>
<tr>
<td>Tricuspid PASP (mm Hg)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=31</td>
<td>38.0 (20 to 55)</td>
<td>n=4</td>
<td>33.0 (25 to 39)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0 (-19 to 32)</td>
<td>n=2</td>
<td>1.0 (1 to 1)</td>
</tr>
<tr>
<td>E/E’ lateral ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=26</td>
<td>13.4 (8.8 to 53.8)</td>
<td>n=9</td>
<td>12.4 (9.7 to 14.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1.3 (-13.1 to 11.9)</td>
<td>n=3</td>
<td>-0.1 (-3.2 to 3.1)</td>
</tr>
<tr>
<td>E/A ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=19</td>
<td>2.7 (0.6 to 4.7)</td>
<td>n=9</td>
<td>2.9 (2.0 to 3.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6 (-0.5 to 1.4)</td>
<td>n=3</td>
<td>0.3 (-0.5 to 1.0)</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=20</td>
<td>74.0 (41 to 105)</td>
<td>n=1</td>
<td>90.0 (90 to 90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.5 (-29 to 28)</td>
<td>n=0</td>
<td>—</td>
</tr>
</tbody>
</table>

PASP indicates pulmonary artery systolic pressure; E/A, ratio of peak mitral early and atrial diastolic contraction velocity; E/E’, ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity; and IVRT, isovolumic relaxation time.

*One patient had no echocardiography assessment at baseline.

‡The number of patients contributing to these outcomes was based on patients having non-missing baseline and Month 12 values.

‡To calculate tricuspid PASP, right atrial pressure (RAP) was estimated based on right atrial (RA) size and inferior vena cava (IVC) size and collapse (normal RA and IVC: RAP estimated as 5 mm Hg; dilated RA and normal IVC: 10 mm Hg; IVC dilated but normal collapse: 15 mm Hg; IVC dilated with reduced or absent collapse: 20 mm Hg).
Supplemental Table 1.6. Holter Monitoring Abnormalities by TTR Genotype

<table>
<thead>
<tr>
<th>Parameter, n/N (%)*</th>
<th>Overall N=35</th>
<th>V122I N=4</th>
<th>Wild-Type N=31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Abnormality</td>
<td>28/34 (82.4)</td>
<td>4/4 (100.0)</td>
<td>24/30 (80.0)</td>
</tr>
<tr>
<td>Atrial Fibrillation/Flutter</td>
<td>6/33 (18.2)</td>
<td>0/3 (0.0)</td>
<td>6/30 (20.0)</td>
</tr>
<tr>
<td>Atrial Tachycardia</td>
<td>14/34 (41.2)</td>
<td>3/4 (75.0)</td>
<td>11/30 (36.7)</td>
</tr>
<tr>
<td>Non-sustained Ventricular Tachycardia (&lt;30 beats)</td>
<td>20/34 (58.8)</td>
<td>3/4 (75.0)</td>
<td>17/30 (56.7)</td>
</tr>
<tr>
<td>Sustained Ventricular Tachycardia (≥30 beats)</td>
<td>0/34 (0.0)</td>
<td>0/4 (0.0)</td>
<td>0/30 (0.0)</td>
</tr>
<tr>
<td>Sinus Pause</td>
<td>2/34 (5.9)</td>
<td>0/4 (0.0)</td>
<td>2/30 (6.7)</td>
</tr>
</tbody>
</table>

*Number with abnormality/Number eligible for assessment (%) at visit.
†One patient had no Holter monitoring test at baseline.
‡Ratios exclude those patients with abnormal values at baseline and give the frequency of treatment-emergent abnormalities.
Supplemental Table 1.7. Summary of Results From Cardiac Magnetic Resonance Imaging in the ITT Population

<table>
<thead>
<tr>
<th>Parameter, median (range)</th>
<th>Baseline</th>
<th>Change from baseline at Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular anteroseptal wall thickness (mm)</td>
<td>n=18 16.1 (9.2 to 23.3)</td>
<td>n=15 1.0 (-3.7 to 6.4)</td>
</tr>
<tr>
<td>Left ventricular inferolateral wall thickness (mm)</td>
<td>n=18 15.3 (9.0 to 25.0)</td>
<td>n=15 1.7 (-9.0 to 8.4)</td>
</tr>
<tr>
<td>Left ventricular mass (g)</td>
<td>n=18 228.5 (133.3 to 389.7)</td>
<td>n=15 -3.8 (-30.5 to 50.0)</td>
</tr>
<tr>
<td>Left ventricular end diastolic volume (mL)</td>
<td>n=18 169.2 (82.7 to 246.8)</td>
<td>n=15 -1.6 (-31.6 to 50.9)</td>
</tr>
<tr>
<td>Left ventricular end systolic volume (mL)</td>
<td>n=18 78.6 (31.1 to 142.8)</td>
<td>n=15 4.8 (-20.3 to 44.2)</td>
</tr>
<tr>
<td>Left ventricular stroke volume (mL)</td>
<td>n=18 80.9 (41.7 to 128.7)</td>
<td>n=15 -6.8 (-43.7 to 13.9)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>n=18 51.9 (26.5 to 62.5)</td>
<td>n=14 -3.4 (-26.3 to 13.5)</td>
</tr>
<tr>
<td>Right ventricular end diastolic free wall thickness (mm)</td>
<td>n=17 7.2 (4.2 to 63.5)</td>
<td>n=15 -0.6 (-15.9 to 3.7)</td>
</tr>
<tr>
<td>Right ventricular end diastolic volume (mL)</td>
<td>n=18 175.0 (53.3 to 356.2)</td>
<td>n=15 11.3 (-63.9 to 72.8)</td>
</tr>
<tr>
<td>Right ventricular end systolic volume (mL)</td>
<td>n=18 110.3 (16.3 to 226.9)</td>
<td>n=15 28.9 (-9.8 to 115.1)</td>
</tr>
<tr>
<td>Right ventricular stroke volume (mL)</td>
<td>n=18 64.9 (23.2 to 129.4)</td>
<td>n=15 -3.0 (-67.9 to 60.4)</td>
</tr>
<tr>
<td>Right ventricular ejection fraction (%)</td>
<td>n=18 43.5 (17.0 to 69.4)</td>
<td>n=15 -10.0 (-27.9 to 14.8)</td>
</tr>
<tr>
<td>Right ventricular end diastolic mass (g)</td>
<td>n=18 63.6 (29.6 to 113.1)</td>
<td>n=15 1.3 (-28.7 to 44.6)</td>
</tr>
</tbody>
</table>

ITT indicates intend to treat.
Supplemental Figure 1.1. Least square (LS) mean change from baseline in cardiac biomarker concentrations in the V122I subpopulation during tafamidis treatment.

(A) At baseline, NT-proBNP concentrations were elevated in the 4 V122I patients (median, 5146 pg/mL; range, 2877 to 5560 pg/mL) and increased beyond Month 3. Similar results were obtained for troponin I (B) and troponin T (C) with raised median baseline values of 0.14 ng/mL (range, 0.14 to 0.14 ng/mL) and 0.07 ng/mL (range, 0.05 to 0.08 ng/mL), respectively. Baseline is defined as the last evaluation prior to the first dose of study drug.
Supplemental Figure 1.2. 6-minute walk test (6MWT) results in the overall intent-to-treat population and the V122I subpopulation over the course of tafamidis treatment.

(A) Categorical analysis of the 6MWT suggests that there was no change in submaximal exercise tolerance during the course of tafamidis treatment in the overall population. Three out of 4 V122I patients’ 6MWT results fell within the worst category (<300 m) at baseline. One wild-type patient did not complete any 6MWT.

(B) The LS mean (±SE) change in distance walked decreased by −30.4 (±44.8) m from baseline to Month 12 in the V122I subpopulation.
Supplemental Figure 1.3. Patient global assessment results in the overall intent-to-treat population and the V122I subpopulation during the course of tafamidis treatment.

A) 75–88% of patients assessed their global status as preserved or improved throughout the study when asked, “How do you feel today as compared to when we talked with you at your last clinic visit for this study?” Change is from previous visit. The functional status of 15.2% of patients was ‘excellent’; of 42.4% ‘very good’; of 36.4% ‘good’; of 6.1% ‘fair’; and of 0% ‘poor’ at baseline based on the question, “In general, how do you feel today?” One wild-type patient had missing Month 3 results.

B) 75% of V122I patients assessed their global status as preserved or improved throughout the study and their functional status at baseline was ‘very good’ (n=1), ‘good’ (n=2), or fair (n=1).
Supplemental Figure 1.4. Results of the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Short Form 36 Quality of Life Questionnaire (SF36) over the course of tafamidis treatment.

(A) Changes from baseline in KCCQ scores in the wild-type and V122I subpopulations. The KCCQ is a heart failure specific questionnaire that quantifies physical limitation, symptoms, quality of life, social interference, and self-efficacy. Scores range from 0 to 100, where higher scores indicate better functioning, fewer symptoms, and better disease-specific quality of life. At baseline, the mean overall summary score was 71.4 (SD: 18.81; n=35) and the mean clinical summary score (calculated by combining the functional status with the QoL and social limitation domains) was 74.1 (SD: 18.86; n=35). Both scores decreased only marginally over the 12 months of tafamidis treatment indicating that functional status and QoL were preserved.

(B) Changes from baseline in SF36 scores in the wild-type and V122I subpopulations. The SF36 comprises 8 health domain scales (physical functioning; role limitations due to physical health; bodily pain; general health; social functioning; role limitations due to emotional problems; mental health; and vitality) that are aggregated into a physical component summary score (PhyCS) and a mental component summary score (MCS). All scores are standardized employing a linear T-score transformation to a mean of 50 and a SD of 10 to provide norm-based scores where a score >50 represents better-than-average function and a score <50 poorer-than-average function, as previously reported. At baseline, the overall patient population demonstrated a lower than average PhyCS of 41.0 (SD: 9.69, n=33) and an average MCS of 52.7 (SD: 9.51; n=35). Overall, changes over time in both these component scores were minimal, demonstrating maintained general quality of life following 12 months of tafamidis treatment.

2. Efficacy outcome results excluding data of the AL amyloidosis patient erroneously diagnosed with wild-type TTR-CM at study entry.

Supplemental Method 2.1. Narrative of Diagnosis of the Patient With AL Amyloidosis

The patient with AL amyloidosis erroneously diagnosed with wild-type TTR-CM at study entry had a monoclonal spike on serum immunofixation, but normal free light chain ratio and 2% plasma cells in the marrow. Immunogold electron microscopy of a cardiac biopsy specimen stained positively for transthyretin without staining for kappa or lambda, and a diagnosis of TTR amyloidosis was made. The patient was TTR stabilized at Week 6 but was re-evaluated following rapid deterioration in status not typical of the progression of TTR-CM. Serum free light chains were repeated, and the free lambda was now markedly elevated. A repeat cardiac biopsy was done, and immunogold electron microscopy now showed staining for lambda light chains without TTR staining. Reanalysis of both biopsy samples by mass spectrometry showed that both were negative for TTR and positive for immunoglobulin light chains. The patient experienced dyspnea on Day 277, worsening heart failure on Day 297, and died on Day 329 due to complications of pleurodesis to treat recurrent pleural effusions.

The importance of identifying the correct amyloid fibril protein after diagnosis of suspected systemic amyloidosis has been previously stressed by Lachmann et al. and the finding that immunogold electron microscopy, a highly specific and established technique, misdiagnosed an AL amyloidosis patient with TTR amyloidosis in this study is an example of the limits of even an established diagnostic test and suggests the use of the most sensitive and accurate method available, currently proteomic analysis using mass spectrometry.

The following tables and figures present efficacy outcome results in the wild-type subpopulation excluding the data from this patient with AL amyloidosis who is not expected to respond to tafamidis treatment.

### Supplemental Table 2.1. TTR Stabilization in the Wild-type Subpopulation When Excluding Data of the Patient With AL Amyloidosis

<table>
<thead>
<tr>
<th>Visit</th>
<th>Wild-Type</th>
<th>N=30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients evaluated, n</td>
<td>30</td>
</tr>
<tr>
<td>Week 6*</td>
<td>Patients stabilized, n (%)</td>
<td>29 (96.7)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>82.8–99.9</td>
</tr>
<tr>
<td>Month 6</td>
<td>Patients evaluated, n</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Patients stabilized, n (%)</td>
<td>26 (89.7)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>72.6–97.8</td>
</tr>
<tr>
<td>Month 12</td>
<td>Patients evaluated, n</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Patients stabilized, n (%)</td>
<td>25 (89.3)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>71.8–97.7</td>
</tr>
</tbody>
</table>

TTR indicates transthyretin; and CI, confidence interval.

*Primary end point.
### Supplemental Table 2.2. Echocardiographic Parameters in the Wild-type Subpopulation When Excluding Data of the Patient With AL Amyloidosis

<table>
<thead>
<tr>
<th>Parameter, median (range)</th>
<th>Baseline*</th>
<th>Change from baseline at Month 12†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventricular septum thickness (mm)</td>
<td>n=29</td>
<td>20.0 (14 to 31)</td>
</tr>
<tr>
<td>LV posterior wall thickness (mm)</td>
<td>n=29</td>
<td>20.0 (14 to 28)</td>
</tr>
<tr>
<td>Right ventricle wall thickness (mm)</td>
<td>n=24</td>
<td>9.5 (4 to 14)</td>
</tr>
<tr>
<td>Left atrial diameter, anterior-posterior (mm)</td>
<td>n=29</td>
<td>44.0 (33 to 60)</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>n=29</td>
<td>50.0 (20 to 70)</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>n=20</td>
<td>37.0 (17 to 51)</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>n=28</td>
<td>24.5 (2 to 43)</td>
</tr>
<tr>
<td>Tricuspid PASP (mm Hg)†</td>
<td>n=27</td>
<td>38.0 (20 to 55)</td>
</tr>
<tr>
<td>E/E’ lateral ratio</td>
<td>n=21</td>
<td>15.4 (8.8 to 53.8)</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>n=15</td>
<td>2.7 (0.9 to 4.7)</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>n=19</td>
<td>74.0 (41 to 105)</td>
</tr>
</tbody>
</table>

PASP indicates pulmonary artery systolic pressure; E/A, ratio of peak mitral early diastolic and atrial contraction velocity; E/E’, ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity; IVRT, isovolumic relaxation time; and SD, standard deviation.

*One patient had no echocardiography assessment at baseline.

†The number of patients contributing to these outcomes was based on patients having non-missing baseline and Month 12 values.

‡To calculate tricuspid PASP, right atrial pressure (RAP) was estimated based on right atrial (RA) size and inferior vena cava (IVC) size and collapse (normal RA and IVC: RAP estimated as 5 mm Hg; dilated RA and normal IVC: 10 mm Hg; IVC dilated but normal collapse: 15 mm Hg; IVC dilated with reduced or absent collapse: 20 mm Hg).
Supplemental Table 2.3. Holter Monitoring Abnormalities in the Wild-type Subpopulation When Excluding Data of the Patient With AL Amyloidosis

<table>
<thead>
<tr>
<th>Parameter, n/N (%)*</th>
<th>Baseline†</th>
<th>Month 12‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Abnormality</td>
<td>23/29 (79.3%)</td>
<td>23/29 (79.3%)</td>
</tr>
<tr>
<td>Atrial Fibrillation/Flutter</td>
<td>6/29 (20.7%)</td>
<td>8/18 (44.4%)</td>
</tr>
<tr>
<td>Atrial Tachycardia</td>
<td>10/29 (34.5%)</td>
<td>0/16 (0.0%)</td>
</tr>
<tr>
<td>Non-sustained Ventricular Tachycardia (&lt;30 beats)</td>
<td>17/29 (58.6%)</td>
<td>4/11 (36.4%)</td>
</tr>
<tr>
<td>Sustained Ventricular Tachycardia (≥30 beats)</td>
<td>0/29 (0.0%)</td>
<td>1/26 (3.8%)</td>
</tr>
<tr>
<td>Sinus Pause</td>
<td>2/29 (6.9%)</td>
<td>5/24 (20.8%)</td>
</tr>
</tbody>
</table>

*Number with abnormality/Number eligible for assessment (%) at visit.
†One patient had no Holter monitoring assessment at baseline.
‡Ratios exclude those patients with abnormal values at baseline and give the frequency of treatment-emergent abnormalities.
Supplemental Figure 2.1. Least square (LS) mean change from baseline in NT-proBNP (A), troponin I (B), and troponin T (C) during tafamidis treatment in the wild-type subpopulation when excluding data of the patient with AL amyloidosis.

Median (range) baseline concentrations were 3201 (820–18401) pg/mL, 0.125 (0.060–0.410) ng/mL, and 0.030 (0.010–0.160) ng/mL, respectively. Error bars represent standard error (SE).
Supplemental Figure 2.2. 6-minute walk test (6MWT) results over the course of tafamidis treatment in the wild-type subpopulation when excluding data of the patient with AL amyloidosis.

(A) Categorical analysis of the 6MWT suggests that there was no change in submaximal exercise tolerance during the course of tafamidis treatment.

(B) The change in the distance walked was minimal with an estimated LS mean (SE) change from baseline of –8.9 (15.5) m at Month 12. One patient did not complete any 6MWT.
Supplemental Figure 2.3. Results of patient global assessment during the course of tafamidis treatment in the wild-type subpopulation when excluding data of the patient with AL amyloidosis.

71–86% of patients assessed their global status as preserved or improved throughout the study when asked, “How do you feel today as compared to when we talked with you at your last clinic visit for this study?” Change is from previous visit and the functional status of 17.9% of patients was ‘excellent’; of 42.9% ‘very good’; of 35.7% ‘good’; of 3.6% ‘fair’; and of 0% ‘poor’ at baseline based on the question, “In general, how do you feel today?” One patient had missing Month 3 results.
Transthyretin 아밀로이드가 침착하는 심근증에서는 Tafamidis 약제가 효과적이다

이 해영 교수 · 서울대학교병원 순환기내과

초록

배경
Transthyretin(TTR) 아밀로이드증(amyloidosis)은 불안정하게 결합된 TTR 단위체에 의해 나타나는 진행성 전신성 질환으로, 아밀로이드가 심장 및 전신에 침착한다.

방법 및 결과
본 단일군 개방형 임상 2상 연구는 tafamidis 약제 20mg을 매일 경구 투여하여, 6주(일차 종료점), 6개월, 12개월에 TTR 분자 안정화 효과를 평가하고, TTR 아밀로이드 심근증에 대한 안전성, 임상 효과를 확인하였다. 31명의 정상 유전자 (wild type) 심부전 환자(중앙 연령 76.7세; 남성 93.5%)를 대상으로 하였는데, 이들의 질병 기간은 중앙값 55.6개월이고, 96.8%가 NYHA(New York Heart Association) I-II 정도의 경-중등도 환자였다. 이들 중 30명(96.8%)에서 투여 6주 후 TTR 분자 안정화 효과가 관찰되었고, 12개월까지 연구 완료된 28명 중 25명(89.3%)에서 TTR 분자 안정화 효과가 지속되었다. 12개월의 치료 기간 중에 3명이 약제 투여를 조기 중단하였고, 2명은 사망하였으며, 7명은 심혈관계 사건으로 입원하였다. 28명 중 20명은 안정된 증상(NYHA 호흡곤란 지표가 같은 수준으로 유지됨)을 보였으나, 31명 중 15명(48.4%)에서는 심부전 입원, 심방세동, 의식 소실 등의 질병 진행 소견이 나타났다. NT-proBNP(N-terminal prohormone brain natriuretic peptide) 혈중 농도는 유의하게 증가하지 않았으나, troponin I와 troponin T는 경도로(moderately) 증가 하였다. 심초음파 소견상 연구 전후의 유의한 변동사항은 관찰되지 않았으며, 31명 중 7명에서 간헐적인 설사가 발생한 것 외에는 유의한 유해 작용이 관찰되지 않았다.

결론
Tafamidis 치료는 TTR 분자를 효과적으로 안정화시켰고, 내 약성이 우수하였다. 그러나 심부전의 생화학 지표 및 심초음파 지표에 대한 유의한 호전 소견은 관찰되지 않았으며, 이에 대한 추가 연구가 필요할 것으로 판단된다.