SUPPLEMENTAL MATERIAL

Cost-Effectiveness of Tafamidis Therapy for Transthyretin Amyloid Cardiomyopathy

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I. Supplemental Methods – Additional Modeling Details.

a. Tafamidis Dose and Pricing:

In the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT), patients were randomized to receive 80 mg tafamidis (four 20mg pills), 20 mg tafamidis, or matching placebo placebo once daily in a 2:1:2 ratio. The trial showed no significant clinical differences between the two tafamidis doses, and FDA approval was based on a comparison between patients receiving either dose of tafamidis compared with those receiving placebo. The manufacturer plans to stop manufacturing 20mg pills by the end of 2019 and transition all patients to a single 61mg capsule of tafamidis meglumine (equivalent to 80mg of tafamidis). The wholesale acquisition cost of an annual supply of tafamidis meglumine 60mg capsules is identical to that of tafamidis 80mg pills, i.e., $225,000 per patient.

b. Adverse Events:

In ATTR-ACT, permanent discontinuation of tafamidis or placebo as a result of adverse events was less common in the tafamidis groups than in the placebo group. Although prior studies had shown an excess in cases of diarrhea and urinary tract infection in patients with familial amyloid polyneuropathy, diarrhea and urinary tract infections were numerically less common in patients who received tafamidis in ATTR-ACT than in those who received placebo. Small numerical differences in treatment-emergent adverse effects may represent chance findings, and were therefore not incorporated into our model.

c. Survival Curves in the Usual Care and Tafamidis Arms:

Supplemental Table 1 summarizes how the modeling assumptions related to survival in the control and intervention arms of the model vary over time.

Supplemental Table 1. Time-Varying Assumptions Regarding Survival in the Control and Intervention Arms of the Model.

Time Period	Survival in the Usual Care (Control) Arm	Survival in the Tafamidis (Intervention) Arm
Up to 18 months	Weibull model fit to observed events in the control arm of ATTR-ACT; parametric bootstrapping used to capture uncertainty due to sampling variation (assuming bivariate normal joint distribution of sigma and k parameters)	Assumed to be equal to the control arm
18 – 30 months	Same as above (Weibull model fit to observed events in the control arm of ATTR-ACT)	Weibull model fit to observed events in the pooled tafamidis arms of ATTR-ACT
Beyond 30 months	Extrapolation based on Weibull model above	The base case applies the hazard ratio (tafamidis vs usual care) observed in month 30 to the projected event rate in the control arm beyond month 30. This assumes a sustained benefit of tafamidis therapy ("best-case scenario") and is varied in scenario analyses. See text for details.

d. Cost of Diagnosing Transthyretin Amyloid Cardiomyopathy (ATTR-CM):

Patients with a new diagnosis of heart failure with preserved ejection fraction receive a battery of tests for establishing the diagnosis and prognosis. Since ATTR-CM is a distinct clinical entity with prognostic implications for the patient and potentially the patient's family members, we assumed that patients with HFpEF would be tested for ATTR-CM regardless of the ultimate decision to treat with tafamidis. The cost of the diagnostic tests is therefore not relevant to establishing the cost-effectiveness of tafamidis relative to usual care (since both groups undergo diagnostic testing). We therefore did not include the cost of diagnostic testing in our analysis. If the availability of a new potential treatment were to substantially increase the uptake of diagnostic testing, this may produce greater total healthcare expenditures, but the one-time cost of diagnostic tests is likely to be extremely small compared with the life-time increase in pharmaceutical spending for tafamidis therapy.

Although diagnostic pathways and hence diagnostic costs may vary substantially among patients and health systems, if we assume unit costs equivalent to Medicare reimbursement for a pyrophosphate scan ($500) and a serum light chain assay ($38), and weight these costs for diagnostic yield (i.e., assuming 4 out of every 100 patients with heart failure and preserved ejection fraction have ATTR-CM and adusting for incident cases of AL amyloidosis), total diagnostic costs would be $12,538 per patient diagnosed with ATTR-CM. This amount is less than the cost of a one-month supply of tafamidis at 2019 prices ($18,750), and substantially less than the lifetime cost of tafamidis therapy for each patient diagnosed with ATTR-CM (i.e., $1,086,000). Thus, in the long run, the budet impact is likely to be driven primarily by pharmaceutical costs among patients diagnosed with ATTR-CM receiving tafamidis therapy rather than expenses related to diagnostic testing.

e. Costs of Cardiovascular and Non-Cardiovascular Care:

We estimated the facility costs of cardiovascular hospitalizations from 2014 Healthcare Cost and Utilization Project (HCUP) data using ICD-9 codes (Supplemental Table 2).[1] The online HCUPnet tool computes facility charges using the National Inpatient Sample (NIS), a nationally representative sample of inpatient hospital discharges that includes over 7 million unweighted and 35 million weighted visits to community hospitals per year. Facility charges in the NIS include data from all payer types (e.g., Medicare, Medicaid, private insurance, and uninsured). The NIS does not include rehabilitation or long-term acute care hospitals.

The HCUPnet tool estimates facility costs in NIS by applying a cost-to-charge ratio.[2] The HCUP Cost-to-Charge Ratio Files are used to estimate the cost of resource use for inpatient hospital stays and its variation across hospitals and conditions based on the reported total charge and the cost ratios provided in the supplemental files. Costs reflect the actual expenses incurred in the production of hospital services, such as wages, supplies, and utility costs; charges represent the amount a hospital billed for the case. Costs are computed from charges using an all-payer inpatient cost-to-charge ratio (created by dividing the inpatient costs by the inpatient charges) when available. When the hospital-specific all-payer inpatient cost-to-charge ratio is not

available, a weighted group-average cost-to-charge ratio (a weighted average for the hospitals in peer groups defined by state, urban/rural, investor-owned/other, and bed size) is used.[2]

Since these facility cost estimates do not include physician fees, we adjusted them by multiplying the facility costs for each hospitalization by a professional fee ratio from Peterson et al.[3] The professional fee ratio was derived as the "ratio of total payments to facility-only payments per admission" from over 23 million inpatient admissions in the Truven Health MarketScan database.[3]

Of note, we found no meaningful difference in the cost of cardiovascular hospitalizations between individuals with or without a prior history of heart failure (data not shown). Although patients with a history of heart failure have more frequent cardiovascular hospitalizations than patients without a history of heart failure, the mean cost of each cardiovascular hospitalization did not differ between the two groups. We therefore included all cardiovascular hospitalizations in this analysis so as to obtain more precise cost estimates.

The Second Panel on Cost-Effectiveness in Health and Medicine recommends that all base case analyses include background healthcare costs – i.e., costs unrelated to the disease being investigated.[4] These costs become particularly salient when evaluating therapies that prolong life among older adults, as is the case with tafamidis. For our study, background costs were estimated using total expenditures for individuals 18 years and older with history of heart failure from the 2006-2015 Medical Expenditure Panel Survey (MEPS), stratified by age.[5] When weighted, MEPS generates nationally representative estimates of healthcare costs and utilization for the US civilian, noninstitutionalized population and includes the amount paid for all payer types (e.g., Medicare, Medicaid, private insurance, patient out-of-pocket costs).

We identified individuals with heart failure from the Medical Conditions file in MEPS using Ninth Revision of International Classification of Diseases (ICD-9) code 428. As cardiovascular events were simulated separately, we excluded individuals with an acute cardiovascular event in the last year or during the survey year. We used a combination of the MEPS Inpatient Stays,

Emergency Room Visits, and Medical Conditions files to identify individuals with acute cardiovascular events. Based on a review of published literature and clinical judgement, we used both ICD-9 codes (Medical Conditions file) and clinical classification codes (CCCs) (Inpatient Stays and Emergency Room Visit files – not all years of these files contained ICD-9 codes) to identify cardiovascular events (Supplemental Table 2). We classified acute cardiovascular events as any: (1) ≥1 inpatient stay with a cardiovascular event in any available CCC position, (2) ≥1 emergency room visit with a cardiovascular event in any available CCC position, or (3) the age of cardiovascular event diagnosis in the Medical Conditions file was ≤1 year from the individual's age at the time of survey.

We estimated the adjusted survey-weighted background healthcare costs using a two-part model, adjusting for selected demographic characteristics and comorbidities. We used two-part models due to the high number of individuals with zero total healthcare expenditures during the survey year. Two-part models are a type of economic analysis that first uses multivariable logistic regression to predict if an individual has non-zero costs. Then, only among individuals with non-zero costs, a multivariable generalized linear model predicts costs. Costs are estimated by multiplying the probability of non-zero costs from the logistic regression by the predicted costs from the generalized linear model regression. Covariates included: age; sex; race; diagnosis of hypertension, hyperlipidemia, and diabetes; BMI; current cigarette smoking; and history of coronary heart disease, myocardial infarction, heart failure, stroke, and cardiac arrest; and number of types of cardiovascular events. We also included interaction terms between sex and race, hypertension and hyperlipidemia, as well as age and the following: race, hypertension, hyperlipidemia, BMI, smoking status, diabetes, and each cardiovascular event type. The logistic regression model had good predictive ability, with an area under the curve of 0.79. We then predicted the background healthcare costs among individuals with heart failure stratified by age (65-74, 75-84, and ≥85 years).

As MEPS does not include institutionalized individuals receiving long-term care, we separately estimated the mean, weighted cost of long-term care, stratified by age. We estimated the proportion of US adults using long-term care in 2013-2014, stratified by age, using data from the

National Study of Long-Term Care Providers and the 2010 US Census.[6,7] We multiplied the proportion of all US adults using each type of long-term care service by published annual long-term care cost estimates from the US Department of Health and Human Services to estimate the mean, weighted cost of long-term care (Supplemental Table 3).[8,9]

To estimate the total background healthcare costs, the appropriate age-specific mean, weighted long-term care costs are added to background healthcare costs estimated from MEPS using the two-part model (Supplemental Table 4). We used per-enrollee estimates from the National Health Expenditures Accounts (NHEA), reported annually by the US Department of Health and Human Services, to determine the credibility of our approach in the overall MEPS population.[10,11] The objective of the NHEA is to estimate the "total annual dollar amount of health care consumption in the US."[10] We used Medicare per-enrollee expenditures for the lower limit and Medicaid for the upper limit for ages 65-84 and ≥85 years.[11] Our approach produced similar estimates to the NHEA in the overall population (Supplemental Table 4).

All costs were inflated to 2019 US dollars using the personal consumption expenditure index.[12]

Supplemental Table 2. Codes Used to Identify Cardiovascular Disease Events in Claims Data.

CVD Event or Comorbidity	ICD or CCC	MEPS Code	HCUP Codes	Description
Myocardial Infarction	ICD-9	410	410.XX, 429.7X	Acute myocardial infarction
	CCC	100	-	Acute myocardial infarction
CHD/Angina	ICD-9	411	411.XX	Other acute and subacute forms of ischemic heart disease
		412	412	Old myocardial infarction
		413	413.X	Angina pectoris
		414	414.01, 414.06, 414.1X,414.2, 414.9	Other forms of chronic ischemic heart disease
	CCC	101	-	Coronary atherosclerosis and other heart disease
Heart Failure	ICD-9	398	398.91	Other rheumatic heart disease
		402	402.X1	Hypertensive heart disease
		404	404.X3, 404.X4	Hypertensive heart and chronic kidney disease
		415	415	Acute pulmonary heart disease
		416	416.9	Chronic pulmonary heart disease
		422	422	Acute myocarditis
		425	425.XX	Cardiomyopathy
		428	428.XX	Heart Failure
	CCC	97	-	Peri-; endo-; and myocarditis; cardiomyopathy (except that caused by tuberculosis or sexually transmitted disease)
		99	-	Hypertension with complications
		103	-	Pulmonary heart disease
		108	-	Congestive heart failure; non-hypertensive
Stroke	ICD-9	430	430	Subarachnoid hemorrhage
		431	431	Intracerebral hemorrhage
		432	432.X	Other and unspecified intracranial hemorrhage
		433	433.XX	Occlusion and stenosis of precerebral arteries
		434	434.XX	Occlusion of cerebral arteries
		436	436	Acute, but ill-defined, cerebrovascular disease
		437	437.X	Other and ill-defined cerebrovascular disease
		438	438.XX	Late effects of cerebrovascular disease
	CCC	109	-	Acute cerebrovascular disease
		110	-	Occlusion or stenosis of precerebral arteries
		111	-	Other and ill-defined cerebrovascular disease
		113	-	Late effects of cerebrovascular disease
Sudden Cardiac Arrest	ICD-9	427	427.5	Cardiac dysrhythmias
	CCC	107	-	Cardiac arrest and ventricular fibrillation
Other Heart Disease	ICD-9	429	429.XX	Ill-defined descriptions and complications of heart disease
	CCC	104		Other and ill-defined heart disease

CCC – Clinical Classification Codes, CHD – coronary heart disease, CVD – cardiovascular disease, HCUP – Health Care Utilization Project, ICD-9 – Ninth Revision of International Classification of Diseases, MEPS – Medical Expenditure Panel Survey.

Supplemental Table 3. Annual Weighted Mean Long-term Care Costs by Age to be Added to Annual Background Healthcare Costs (2019 US Dollars).

Age Category	Base-case	Lower Limit	Upper Limit
<65	$130	$126	$133
65-74	$1,183	$1,152	$1,214
75-84	$3,667	$3,568	$3,765
≥85	$13,574	$13,204	$13,945

Supplemental Table 4. Total Annual Background Healthcare Costs Compared to US Department of Health and Human Service Estimates (2019 US Dollars).

Age Category	MEPS Background Costs	Long-term Care Costs	Total Background Costs	National Health Expenditure Accounts Per-enrollee Estimate[11]
Overall				
65-74	$8,557	$1,183	$9,740	$10,481 – $12,316*
75-84	$9,953	$3,667	$13,620	
≥85	$10,279	$13,574	$23,853	$18,535 – $28,699*
Individuals with Heart Failure				
65-74	$19,785	$1,183	$20,968	N/A
75-84	$18,462	$3,667	$22,129	N/A
≥85	$17,417	$13,574	$30,991	N/A

*Estimated per-enrollee expenditures for Medicare (lower limit) and Medicaid (upper limit)

f. Estimating Quality-of-Life Parameters:

ATTR-ACT used the overall score of the Kansas City Cardiomyopathy Questionnaire (KCCQ-OS) to measure study participants' perception of their health status, symptoms, physical and social function, and quality-of-life, at baseline and during follow-up.[13] The mean (± standard deviation) baseline KCCQ-OS was 65.90±21.74 among patients in the control arm and 67.27±21.36 among patients in the intervention arm. Over the course of 30 months, mean decline in KCCQ-OS was significantly greater among patients in the control arm compared with patients in the intervention arm (20.81±1.97 vs 7.16±1.42). In order to map KCCQ-OS scores to quality-of-life weights, we used individual-level data from a prospective, 14-center cohort of 476 outpatients with heart failure who were assessed at baseline and 6±2 weeks and compared changes in heart failure measures (including KCCQ-OS and EuroQoL-5 Dimension [EQ-5D] health status) with clinically observed changes.[14]

We used a linear regression model to identify the relationship between KCCQ-OS and EQ5D-derived utility weights, using the model

$$\text{Health state utilities} = \alpha + \beta * \text{KCCQOS}$$

We estimated mapping parameters α (intercept) and β (slope), with good model performance ($R^2 = 0.52$). We used these mapping parameters to convert observed KCCQ-OS values from ATTR-ACT to quality-of-life weights for the model (Supplemental Table 5). To capture the uncertainty in this mapping process, we used parametric bootstrapping to generate 10,000 paired values for the mapping parameters, which we then incorporated into the probabilistic sensitivity analysis.[15] Supplemental Table 6 shows the quality-of-life weight changes in the base case analysis over the duration of the simulation in each arm.

Supplemental Table 5. Mapping KCCQ-OS to health-related quality-of-life weights.

Parameter Estimates				Covariance Matrix		
	Point Estimate	Standard Error			α	β
α	0.428986	0.013753		α	0.00018919	-0.00000254101
β	0.005228	0.000194		β	-0.00000254101	0.0000000374694

Of note, we explored a number of alternative models (linear regression, two-part linear/logistic regression, cumulative probability model, item-specific models) and tested for nonlinear effects using natural splines (more flexible than just adding quadratic terms). In no case was there appreciable deviation from linearity, and overall average predictive performance was virtually identical for all models, with R^2 values in the 0.50-0.52 range. We selected the linear regression model here with a linear effect for OS for simplicity of calculation, since it performed as well as the more complex models.

Supplemental Table 6. Improvement in Quality-of-Life with Tafamidis Therapy (Base-Case Analysis).

	Usual Care, mean (95%UI)	Tafamidis, mean (95%UI)
Baseline	0.788 (0.765 – 0.811)	0.788 (0.765 – 0.811)
1 year	0.744 (0.720 – 0.769)	0.773 (0.749 – 0.797)
5 years	0.570 (0.521 – 0.618)	0.713 (0.676 – 0.751)
10 years	0.439 (0.411 – 0.467)	0.638 (0.574 – 0.701)

g. Approach to the Budget Impact Analysis

For estimating the effect of tafamidis adoption on total healthcare spending, we estimated a target population of 120,000 US adults, based on a conservative estimate that 4% of adults older than 60 years who have HFpEF have ATTR-CM. This prevalence estimate was based on a study that systematically screened consecutive HFpEF inpatients, age ≥ 60 years old with left ventricular wall thickness ≥ 1.2 cm with ^{99m}Tc-DPD scintigraphy (a test with high sensitivity and specificity for the diagnosis of ATTR-CM) and found that 13% of the patients had ATTR-CM.[16] These criteria (age ≥ 60 years and wall thickness ≥ 1.2 cm) were then applied to a systematic observational study of HFpEF[17] (all ages and wall thicknesses), resulting in an estimated overall prevalence of 4% among patients with HFpEF. The current estimate of the prevalence of HF in

the US is approximately ~6 million[18], of which 50% (~3 million) are thought to have HFpEF. Thus, 4% of the 3 million HFpEF patients would result in a prevalence of 120,000. This prevalence estimate is similar to prior estimates of 100,000 US adults with ATTR-CM, the number that was used to qualify the condition as a rare disease as part of the FDA's expedited approval process for tafamidis.

We triangulated our prevalence estimate by comparing it with the subset of patients from United States, Argentina, Brazil, and Canada in the Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function study (TOPCAT Americas, n=1767). In TOPCAT Americas, there were 646 patients with an echocardiogram and a measurable left ventricular wall thickness.[19] Of these 646 patients, 283 (43.8%) were age 60 years or older and had either septal or posterior wall thickness ≥ 1.2cm. Next, assuming that 13% of these 283 patients had ATTR-CM (based on the above study), we estimate that 37 of 646 patients (5.7%) with HFpEF in TOPCAT Americas would meet the eligibility criteria for ATTR-ACT. Using the current estimate of HFpEF in the US (~3 million, see above) give us 5.7% x 3,000,000 =171,000 cases of ATTR-CM in the US.

These prevalence estimates are likely underestimates because: 1) Increasing awareness of ATTR-CM among clinicians, widespread availability of scintigraphy to diagnose ATTR-CM, and increased uptake of genetic screening of family members of probands is likely to increase diagnosis rates in the future, 2) Prolonged survival with tafamidis treatment may also increase prevalence over the long-term. We therefore varied the prevalence between 100,000 to 200,000 in sensitivity analyses.

Next we estimated the total (undiscounted) increase in healthcare spending over 5 years for every patient treated with tafamidis, which was used to compute annual change in healthcare spending among patients receiving tafamidis therapy. We then multiplied the annual cost with the number of eligible patients per year to estimate the net change in healthcare spending after tafamidis adoption.

II. Model Calibration

We compared the mean model outputs from 1000 probabilistic iterations of the model at 30 months to published results from ATTR-ACT. We reported uncertainty in the model outputs using the 95% uncertainty interval (i.e., 2.5th to 97.5th percentile of 1000 iterations).We compared outcomes in the tafamidis arm with the control arm by computing the hazard ratio (HR) for all-cause mortality (using a Cox model) and the relative risk ratio for cardiovascular hospitalization (using a Poisson regression model) for each model iteration. The results are shown in Supplemental Table 7.

Supplemental Table 7. Model Calibration.

Calibration Measure	**Simulation Model Output** (95% UI)*	**ATTR-ACT Results** (95% CI where available)§	**Difference** (95% UI)
Mortality at 30 months			
Placebo	41.5% (32.7% – 49.7%)	42.9%	-1.4% (10.2% – 6.8%)
Tafamadis	29.6% (21.7% – 36.4%)	29.5%	0.1% (-7.8% – 6.9%)
All-Cause Mortality HR	0.68 (0.51 – 0.86)	0.70 (0.51 – 0.96)	-
CV Hospitalizations per year			
Placebo	0.69 (0.60 – 0.78)	0.70	-0.01 (-0.10 – 0.08)
Tafamadis	0.49 (0.38 – 0.59)	0.48	0.01 (-0.10 – 0.11)
Relative Risk Ratio	0.70 (0.59 – 0.83)	0.68 (0.56 – 0.81)	-

ATTR-ACT – Transthyretin Amyloidosis Cardiomyopathy Clinical Trial, CI – confidence interval, CV – cardiovascular, HR – hazards ratio, UI – uncertainty interval (2.5th to 97.5th percentile).
*Simulation model output means and 95% UIs derived from 1000 probabilistic model iterations.
§ATTR-ACT did not report confidence intervals for mortality at 30 months and cardiovascular hospitalizations per year for each study arm.

III. Additional Results

Supplemental Table 8. Base-Case Results When Varying Time Horizon.

	Usual Care	Tafamidis
Healthcare Outcomes		
Survival, *life years (discounted)*		
30 months	2.06 (1.94 – 2.20)	2.14 (2.01 – 2.27)
Lifetime	3.23 (2.73 – 3.84)	4.83 (3.82 – 5.79)
Quality-adjusted survival, *QALYs (discounted)*		
30 months	1.52 (1.42 – 1.64)	1.65 (1.54 – 1.76)
Lifetime	2.19 (1.94 – 2.56)	3.48 (2.85 – 4.15)
CV Hospitalizations, *number*		
30 months	1.42 (1.23 – 1.63)	1.00 (0.79 – 1.25)
Lifetime	2.36 (1.87 – 3.02)	2.53 (1.78 – 3.43)
Direct Healthcare Costs		
Total Healthcare Costs, *2019 USD (discounted)*		
30 months	79,000 (71,000 – 88,000)	555,000 (521,000 – 590, 000)
Lifetime	126,000 (105,000 – 157,000)	1,262,000 (996,000 – 1,515,000)
Spending on Tafamidis		
30 months	-	481,000 (452,000 – 511,000)
Lifetime	-	1,086,000 (861,000 – 1,303,000)
Spending on CV Hospitalizations		
30 months	23,000 (18,000 – 29,000)	16,000 (12,000 – 21,000)
Lifetime	34,000 (26,000 – 46,000)	34,000 (23,000 – 47,000)
Background Healthcare Costs		
30 months	56,000 (52,000 – 60,000)	58,000 (54,000 – 63,000)
Lifetime	92,000 (77,000 – 113,000)	142,000 (110,000 – 174,000)
ICER, $ per QALY gained		
30 months	Comparator	$3,903,000 (2,944,000 – 5,685,000)
Lifetime	Comparator	$880,000 (697,000-1,564,000)

CV – cardiovascular, ICER – incremental cost-effectiveness ratio, QALY – quality-adusted life year, USD – United States dollar.

Supplemental Table 9. Sensitivity Analyses. The base-case analysis assumed that the effectiveness of tafamidis on survival, quality-of-life, and rate of cardiovascular hospitalizations as observed in the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial would be sustained over the remainder of the patients' lifetimes. We varied the durability of this effectiveness in sensitivity analyses by modeling an intermediate case, which assumed that that the effectiveness of tafamidis would wane linearly between months 30 and 90, and a worst case, which assumed that tadamidis would be completely ineffective beyond 30 months. Each of these assumptions resulted in fewer projected health gains and higher incremental cost-effectiveness ratios compared with the base case.

	Base Case	Intermediate Case*	Worst Case
Incremental life-years *(discounted)*	1.60	0.61	0.31
Incremental QALYs *(discounted)*	1.29	0.63	0.26
Incremental healthcare costs *(2019 USD, discounted)*	$1,135,000	$930,000	$801,000
ICER, $ per life-year gained	$709,000	$1,146,000	$2,579,000
ICER, $ per QALY gained	$880,000	$1,517,000	$3,122,000

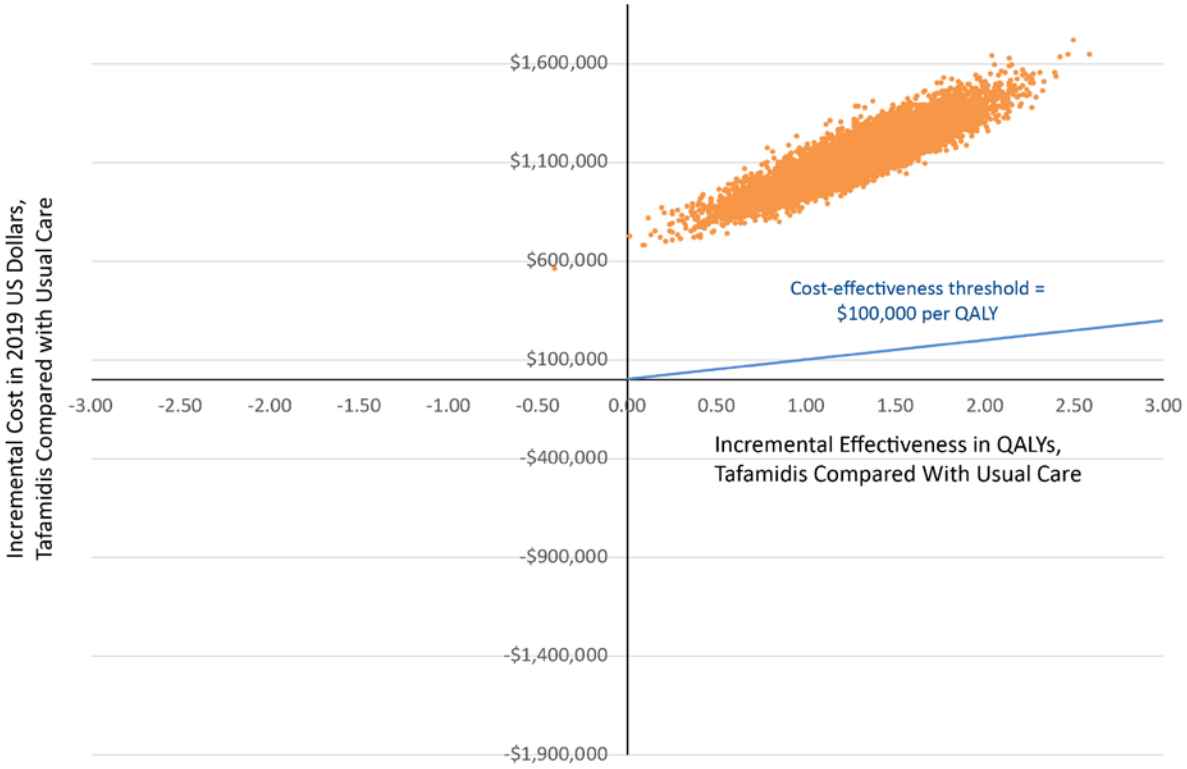
ICER – incremental cost-effectiveness ratio, QALY – quality-adjusted life year.
*The intermediate case assumes that the effectiveness of tafamidis wanes linearly between months 30 and 90, so that by month 90 there is no clinical difference between the intervention and control arms.

Supplemental Table 10. Threshold Analyses. In one-way sensitivity analyses, we explored the reduction in annual cost of tafamidis therapy that would be needed to achieve cost-effectiveness thresholds of $50,000 per QALY gained, $100,000 per QALY gained, and $150,000 per QALY gained under varying assumptions about the durability of effectiveness of tafamidis. Percentage price reductions are calculated from the wholesale acquisition cost of tafamadis in September 2019 ($225,000).

	Annual cost (% price reduction) of tafamidis to meet the specified cost-effectiveness threshold		
Cost-Effectiveness Threshold, *2019 USD per quality-adjusted life year*	Base Case	Intermediate Case	Worst Case
$50,000	$3,200 (98.6%)	$2,179 (99.0%)	$2,183 (99.0%)
$100,000	$16,563 (92.6%)	$9,774 (95.7%)	$5,809 (97.4%)
$150,000	$29,925 (86.7%)	$17,369 (92.3%)	$9,435 (95.8%)

USD – United States dollar.

Supplemental Figure 1. Cost-Effectiveness Plane.



QALY – quality-adjusted life year.

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