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ORIGINAL RESEARCH

Real-World Effectiveness of High-Dose Tafamidis on Neurologic Disease Progression in Mixed-Phenotype Variant Transthyretin Amyloid Cardiomyopathy

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ABSTRACT

Introduction: Transthyretin amyloidosis (ATTR) is a progressive, heterogeneous rare disease manifesting as ATTR polyneuropathy (ATTR-PN), ATTR cardiomyopathy (ATTR-CM), or a mixed phenotype. Tafamidis meglumine (20 mg po qd) is approved in some markets to delay neurologic progression in ATTR-PN, while high-dose tafamidis (80/61 mg po qd) is approved worldwide to reduce cardiovascular mortality and cardiovascular-related hospitalization in ATTR-CM. The objective of this study was to assess the real-world benefit of high-dose tafamidis for delaying neurologic progression in patients with mixed-phenotype variant ATTR-CM (ATTRv-CM).

Methods: This exploratory, retrospective, observational cohort study evaluated anonymized electronic medical records and included adult patients with mixed-phenotype ATTRv-CM treated with high-dose tafamidis for at least 6 months. Neurologic assessments included the Medical Research Council (MRC) Scale for Muscle Strength, Neuropathy Impairment Score (NIS) muscle weakness subscale, and Polyneuropathy Disability (PND) instrument. Modified body mass index (mBMI) was also assessed.

Results: Patients ($N = 10$) started tafamidis treatment an average of 3.8 months after diagnosis, with an average treatment duration of 20.8 months. Seven of 10 patients demonstrated

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normal muscle strength on the MRC scale throughout the study, and 9 of 10 patients had no decline in muscle strength during the post-treatment period. The NIS muscle weakness subscale score was ≤ 60 for all patients in the study at all time points, suggesting normal function to mild impairment. Six of 10 patients had no change in walking capacity as measured by the PND instrument at pre- and post-assessments, while one-third of patients had a decrease in PND stage (signaling improvement) from pre- to post-assessment. mBMI remained relatively stable throughout the study.

Conclusion: This is the first real-world study to demonstrate the potential value of high-dose tafamidis for delaying neurologic disease progression in patients with mixed-phenotype ATTRv-CM. The findings underscore the importance of multidisciplinary assessment for patients with ATTR amyloidosis.

Trial registration: ClinicalTrials.gov: NCT05139680.

Keywords: ATTR amyloidosis; ATTR cardiomyopathy; ATTR polyneuropathy; Real-world; Tafamidis

Key Summary Points

Why carry out this study?

Limited data exist on the impact of high-dose tafamidis on neurologic disease progression in transthyretin amyloidosis cardiomyopathy variant (ATTRv-CM). For patients with mixed-phenotype ATTRv-CM, an understanding of the value of high-dose tafamidis with respect to neurologic disease progression is needed.

What was learned from the study?

High-dose tafamidis treatment delayed neurologic disease progression in patients with mixed-phenotype ATTRv-CM.

INTRODUCTION

Transthyretin amyloidosis (ATTR) is a progressive, life-threatening, and heterogeneous rare disease caused by the deposition of transthyretin-derived amyloid fibrils in the peripheral nerves, heart, and other organs [1, 2]. ATTR amyloidosis may arise from variants (mutations) in the transthyretin (TTR) gene (ATTRv) or from aggregation of age-related non-mutated wild-type TTR (ATTRwt). ATTR amyloidosis is recognized as a spectrum of disease that can manifest as ATTR cardiomyopathy (ATTR-CM), ATTR polyneuropathy (ATTR-PN), or a mixed phenotype, depending on the TTR variant, amyloid deposition pattern, and multisystem involvement [3, 4].

Tafamidis is a first-in-class highly specific and selective stabilizer of both wild-type and amyloidogenic variants of TTR [5] approved outside the United States for the treatment of ATTR-PN (20 mg formulation) and worldwide for the treatment of ATTR-CM (80 mg or the free acid bioequivalent 61 mg "high-dose" formulation) [6]. Tafamidis binds to TTR at the thyroxine-binding site and inhibits TTR tetramer dissociation, the rate-limiting step in the amyloidogenic process [7]. The efficacy and safety of tafamidis for treating ATTR-CM are supported by a clinical development program including one controlled and two uncontrolled studies in patients with ATTRv or ATTRwt cardiomyopathy [8–10]. Findings from the controlled study [10], the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT; NCT01994889), showed a reduction in all-cause mortality and a lower rate of cardiovascular-related hospitalizations with tafamidis versus placebo. As neurologic endpoints were not evaluated in the clinical development program for ATTR-CM, real-world evidence is needed to examine the impact of high-dose tafamidis on neurologic disease progression. The objective of this exploratory study was to assess the benefit of high-dose tafamidis for delaying neurologic disease progression in mixed-phenotype ATTRv-CM in real-world clinical practice.

METHODS

Study Design and Subjects

This was an exploratory, retrospective, observational cohort study (NCT05139680) using structured secondary anonymized data from electronic medical records at MedStar Health. Patients with mixed-phenotype ATTRv-CM receiving tafamidis 61 mg orally once daily for at least 6 months were identified. The study data were extracted and evaluated from three assessment windows. The pre-treatment assessment was 6–12 months prior to the date of tafamidis treatment initiation (index date). The tafamidis initiation assessment window was from 3 months before to 3 months after the start of tafamidis treatment (baseline). The post-treatment assessment window was 6–12 months after tafamidis initiation (Fig. 1).

This study was approved by the MedStar Health Research Institute Institutional Review Board (IRB) (IRB ID: STUDY00006170) and granted a waiver from informed consent. The study followed Good Pharmacoepidemiology Practices guidelines and the principles of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Patients included in this study were at least 18 years of age, diagnosed with hereditary mixed-phenotype ATTRv-CM, and treated with tafamidis (61 mg capsule, orally once daily) for ≥ 6 months (with a ± 3-month window), with at least one neurologic assessment pre- and post-tafamidis treatment. Polyneuropathy was diagnosed on the basis of clinical evidence of neuropathy and electrophysiological diagnostics. Patients were excluded from the study if they had a history of organ transplant or wild-type TTR genotype; were non-ambulatory; had prior treatment with any disease-modifying therapy (investigational or approved) alone or in combination, except tafamidis; or had peripheral neuropathy attributed to causes other than ATTR amyloidosis (e.g., diabetes mellitus, B12 deficiency, HIV infection).

Variables

Exposure Variables

Tafamidis treatment was characterized as follows: Time to treatment initiation was calculated

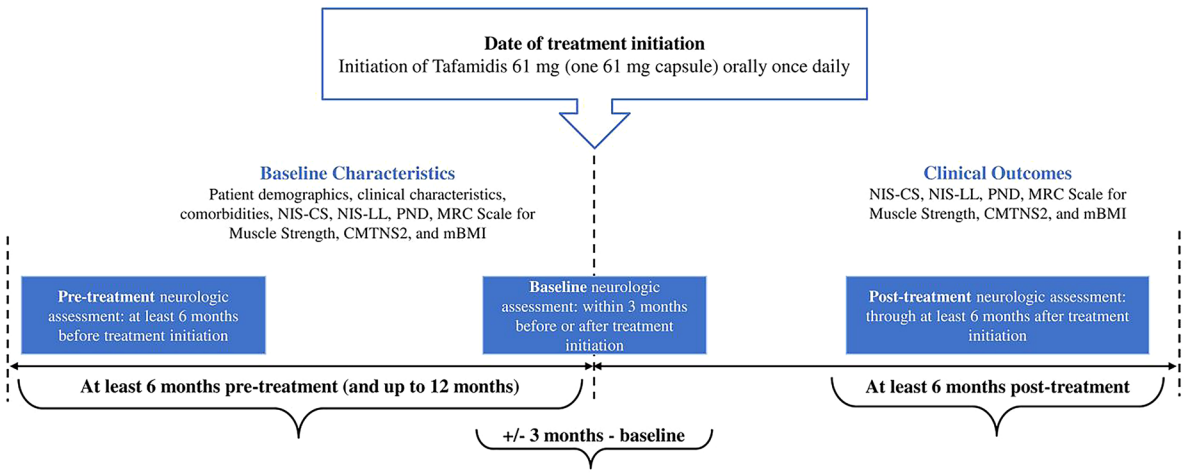

Fig. 1 Study design overview. CMTNS2, Charcot-Marie-Tooth Neuropathy Score v2; mBMI, modified body mass index; MRC, Medical Research Council; NIS-CS, Neuropathy Impairment Score–Composite Score; NIS-LL, Neuropathy Impairment Score–Lower Limbs; PND, Polyneuropathy Disability instrument

as the time from ATTRv-CM diagnosis to tafamidis initiation. Treatment duration was calculated as the time from tafamidis treatment initiation to the end of treatment or last visit.

Outcome Variables

The primary study endpoint was neurologic disease progression, as assessed by the Neuropathy Impairment Score–Composite Score (NIS-CS), the Neuropathy Impairment Score–Lower Limbs (NIS-LL), the Polyneuropathy Disability (PND) score, the Medical Research Council (MRC) Scale for Muscle Strength, and the Charcot-Marie-Tooth Neuropathy Score v2 (CMTNS2).

The NIS-CS assesses motor strength, muscle stretch reflexes, and sensation to arrive at a composite score ranging from 0 (normal) to 244 (total impairment). The NIS-LL assesses motor strength, muscle stretch reflexes, and sensation in the lower body, with a score ranging from 0 (normal) to 88 (total impairment). The PND assesses walking capacity, classifying patients in stages from 0 (no impairment) to IV (confined to a wheelchair or bedridden). The MRC measures muscle strength on a scale of 0–5, with higher scores signaling greater strength. The CMTNS2 classifies patients as having mild, moderate, or severe impairment according to the summed scores for nine components, with higher scores indicating greater impairment.

The secondary study endpoint was mBMI, an indicator of overall health status. mBMI is calculated as the product of BMI in kg/m^2 and serum albumin in g/L to compensate for peripheral edema.

Patient Demographics, Clinical Characteristics, and Comorbidities

Patient demographics, clinical characteristics, and comorbidities in the pre-treatment baseline period were collected. They included but were not limited to sex, age, race, and TTR genotype.

Statistical Analysis

Continuous and categorical variables were reported descriptively using summary statistics. Descriptive analysis for continuous outcomes included mean, standard deviation (SD), median, range, and interquartile range (IQR). Frequencies and percentages were reported for categorical and ordinal outcomes. Primary and secondary outcomes were collected at multiple time points. Measures were reported in the pre-treatment baseline period (at least 6 months and up to 12 months before tafamidis initiation), at tafamidis initiation (±3 months), and in the post-treatment period (at least 6 months after tafamidis initiation with a ± 3-month window). In practice, the final data collected for neurological assessments and mBMI reflected pre- and post-treatment time periods only. Pre- and post-treatment comparisons were not conducted for all neurologic function scales where data were missing. Pre- and post-treatment scores for the MRC, PND, NIS muscle weakness subscale, and mBMI were reported. All analyses were conducted using SAS version 9.4 software (SAS Institute, Inc., Cary, NC).

RESULTS

Fifty-six patients were screened, and 10 patients were included in the study (see CONSORT diagram, Fig. 2). Equal numbers of male and female patients were included in the study, and 80% of the patients were > 65 years of age and African American. The most common genotype was Val122Ile (80.0%), and history of cardiovascular and renal conditions were reported in ≤ 20.0% of patients (Table 1). Patients started treatment with tafamidis an average of 3.8 months (range 0.0–17.0 months) after diagnosis, and the average duration of tafamidis treatment was 20.8 months (range 9.0–33.0 months) (Table 2).

Seventy percent (7/10) of patients demonstrated normal muscle strength on the MRC scale at pre- and post-assessment, and 90% (9/10) exhibited no decline in muscle strength during the post-treatment period. Additionally, the MRC scale score for muscle strength was ≤ 60 for all patients in the study at all time points, suggesting normal function to mild impairment. While two pre-treatment NIS muscle weakness subscale scores were missing, all recorded

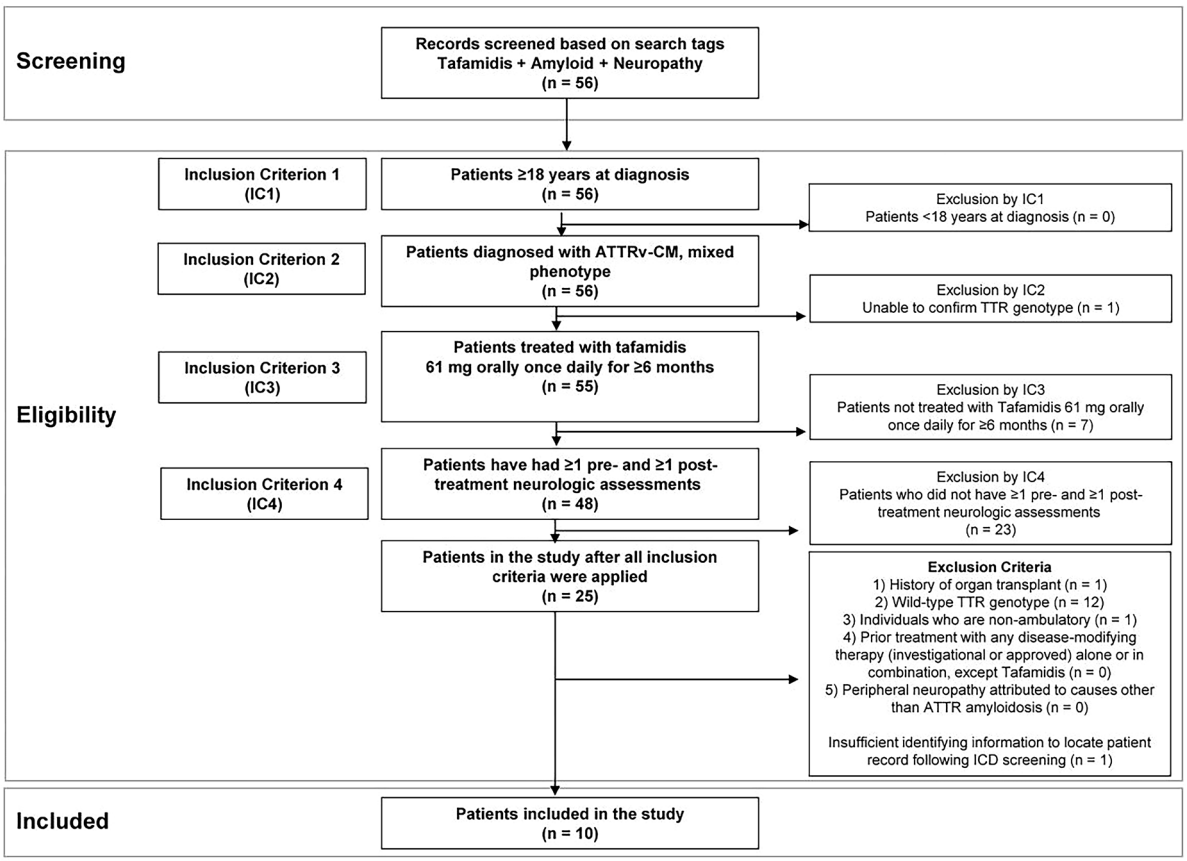

Fig. 2 CONSORT diagram. ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ICD, International Classification of Diseases; TTR, transthyretin

pre-treatment scores also indicated normal function to mild impairment. Among seven patients with recorded NIS muscle weakness subscale scores for both the pre- and post-treatment periods, one patient had an increase of two points and another patient an increase of five points (signaling increased impairment). Five patients had no change or a nominal decrease (signaling improvement) in their NIS muscle weakness subscale scores (Table 3). On the PND, 60% (6/10) of patients had no change in walking capacity between the pre-assessment and post-assessment periods, and 30% (3/10) had a decrease in PND stage from pre- to post-treatment, signaling improvement; one patient moved from stage I to stage II, reflecting a decrease in walking capacity. Due to missing data, scores for the NIS-CS, NIS-LL, CMTNS2, and the NIS-CS subscales for reflex and sensation could not be calculated. The mean mBMI remained relatively stable across the study period: the mean (SD) pre-treatment mBMI was 1001.1 (269.5), and the post-treatment mBMI was 1070.9 (232.6).

DISCUSSION

This is the first exploratory study to report on the real-world effectiveness of high-dose tafamidis for delaying neurologic disease progression in patients with mixed-phenotype ATTRv-CM. In this small sample of mostly older Val122Ile African American patients with mixed-phenotype ATTRv-CM receiving tafamidis 61 mg, neurologic function generally remained stable over the study period. In addition, mBMI remained stable.

Table 1 Baseline demographic and clinical characteristics among patients with ATTRv-CM

Patient characteristics	*N* = 10
Age at baseline, years (mean ± SD)	72.20 ± 10.26
Age group (years), *N* (%)	
18–55	1 (10.0%)
55–65	1 (10.0%)
65–75	3 (30.0%)
≥ 75	5 (50.0%)
Sex, *N* (%)	
Female	5 (50.0%)
Male	5 (50.0%)
Race, *N* (%)	
African American	8 (80.0%)
White	1 (10.0%)
Not reported	1 (10.0%)
Ethnicity, *N* (%)	
Non-Hispanic	1 (10.0%)
Unknown	9 (90.0%)
Age at ATTRv-CM diagnosis, years (mean ± SD)	71.60 ± 10.10
TTR genotype, *N* (%)	
Ala120Ser	1 (10.0%)
Val122Ile	8 (80.0%)
Val30Met	1 (10.0%)
Family history, *N* (%)[a]	
Hypertension	5 (50.0%)
Cardiovascular disease/ coronary artery disease/ chronic obstructive pulmonary disease/ congestive heart failure	4 (40.0%)
Other[b]	3 (30.0%)
Unknown	7 (70.0%)
Congestive heart failure, *N* (%)	
No	8 (80.0%)
Yes	2 (20.0%)
Peripheral vascular disease, *N* (%)	
No	9 (90.0%)
Yes	1 (10.0%)
Cerebrovascular disease, *N* (%)	
No	9 (90.0%)
Yes	1 (10.0%)
Renal disease, *N* (%)	
No	9 (90.0%)
Yes	1 (10.0%)

ATTRv-CM, variant transthyretin amyloid cardiomyopathy, *TTR* transthyretin, *SD* standard deviation

[a]Categories in this variable are not mutually exclusive. A patient could report family history for more than one condition

[b]Other included multiple myeloma, lung cancer, mental illness, osteoarthritis, ovarian cancer, stroke, dementia, type 2 diabetes mellitus, bleeding disorder, and breast cancer

The characteristics of patients in this study were similar to those reported in previous studies of patients with ATTRv-CM. Patients were similar in terms of age at diagnosis (ranging from 70 to 77 years), race (largely African American), and genotype (Val122Ile) [4, 11]. While historically the Val122Ile genotype has been considered a predominantly cardiac phenotype, a recent analysis described the mixed phenotype cohort in the Transthyretin Amyloidosis Outcomes Survey (THAOS) and confirms the findings in the present study. Approximately one-third of symptomatic patients (n = 1185/3542; 33.5%) were classified at enrollment or follow-up as mixed phenotype. Of those classified as mixed phenotype, 88 (7.4%) were V122I ATTR [12].

The findings from this study demonstrating the benefit of tafamidis 61 mg for delaying neurologic disease progression in mixed phenotype ATTRv-CM are consistent with previous evaluations of the efficacy of tafamidis 20 mg for treating ATTR-PN [12–16]. Prior research has also demonstrated the value of early initiation of tafamidis for delaying neurologic disease

Table 2 Treatment patterns among patients with ATTRv-CM

Variable	*N* = 10
Age at tafamidis initiation, years (mean ± SD)	72.0 ± 10.28
Time to treatment initiation (months)[a]	
Mean ± SD	3.80 ± 4.89
Median (Q1 to Q3)	2.0 (1.0–4.0)
Range	0.0–17.0
Duration of treatment (months)[b]	
Mean ± SD	20.80 ± 8.32
Median (Q1 to Q3)	22.0 (14.0–26.0)
Range	9.0–33.0

ATTRv-CM variant transthyretin amyloid cardiomyopathy, *SD* standard deviation, *Q1* lower quartile, *Q3* upper quartile

[a]Time to treatment initiation was defined as time from ATTRv-CM diagnosis to tafamidis initiation

[b]Duration of treatment was defined as time from treatment initiation to the end of treatment, death date, or last visit date, whichever came first

progression [12, 13]. In the present real-world study, where patients generally demonstrated delayed neurologic disease progression, the average latency from diagnosis to treatment initiation was short (3.8 months on average), also reinforcing the benefit of earlier tafamidis initiation.

Strengths of this study include the analysis of patients receiving high-dose tafamidis in clinical practice assessed using standard clinical protocols at an amyloidosis center. Moreover, patients in this study were treated with tafamidis for an average of almost 2 years, providing sufficient time to assess the impact on neurologic disease progression. The study also has several limitations. The analysis was exploratory in nature, and additional studies with a larger number of patients are warranted. The data were derived from a single study site and may not necessarily represent the more heterogeneous group of patients with mixed-phenotype ATTRv-CM worldwide. This was a retrospective study based on a review of electronic medical records, and incomplete data precluded the calculation of some neurologic outcome measures. Finally, the MRC scale score for muscle strength, the PND, and the NIS muscle weakness subscale score are examiner-dependent and subjective in nature. This potential bias may limit the generalizability of the study findings to all patients with ATTRv-CM.

CONCLUSION

This real-world evaluation underscores the value of high-dose tafamidis for delaying neurologic disease progression and maintaining overall health status in patients with mixed-phenotype ATTRv-CM. The findings also reinforce the need for multidisciplinary team care for these complex patients with ATTR amyloidosis. Finally, this study reflects many of the challenges of conducting research in real-world clinical settings, including identifying eligible patients and managing missing data. Further research on the benefits of high-dose tafamidis treatment in patients with mixed-phenotype ATTRv-CM is warranted.

Table 3 Baseline patient characteristics and treatment responses on select measures pre- and post-initiation of tafamidis

Patient ID	A		B		C		D		E		F		G		H		I		J	
Age at baseline, years	86		83		80		75		74		67		77		60		54		66	
Genotype	Val122Ile		Val122Ile		Val122Ile		Val122Ile		Val122Ile		Val122Ile		Val122Ile		Val122Ile		Val30Met		Ala120Ser	
Sex	Female		Female		Male		Female		Female		Male		Male		Male		Male		Female	
Race	African American		White		African American		African American		African American		African American		African American		African American		Not reported		African American	
Time on tafamidis, months	12		26		24		14		9		33		32		22		14		22	
Assessments	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
MRC	60	60	60	60	60	60	60	60	55	55	60	60	60	60	60	54	60	60	46	54
PND	III	I	I	I	I	II	I	I	III	III	II	I	I	I	II	II	I	I	II	I
Muscle weakness (NIS subscale)	–	0	13	2	0	5	2	0	21	21	2	0	0	2	0	–	2	2	–	–
mBMI	798.5	843.1	1063.0	1022.1	906.9	853.7	694.9	953.4	901.8	929	1051.5	1281.9	834.2	1102.2	1571.1	1233.7	1343.1	1575.8*	845.6	914.3

mBMI modified body mass index, *MRC* Medical Research Council, *NIS* Neuropathy Impairment Score, *PND* Polyneuropathy Disability instrument

*Patient missing post-treatment albumin value. For purpose of analysis, the pre-treatment albumin value was used to calculate post-treatment mBMI

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Author Contributions. Nicholas Streicher, Leslie Amass, Jennifer M. Stephens, and Farooq H. Sheikh: contributed to the study conception and design. Nicholas Streicher and Emma Merrill: conducted data collection for the study. Rong Wang, Traci LeMasters, and Rutika Raina: developed the statistical analysis plan. Traci LeMasters and Rutika Raina: performed data analysis. All authors participated in drafting and revising the manuscript and approved the final version.

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Data Availability. Upon request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/data-and-results for more information.

Declarations

Conflict of Interest. Leslie Amass and Rong Wang are employees of Pfizer Inc. and own Pfizer stock. Jennifer M. Stephens, Traci LeMasters, and Rutika Raina are employees of OPEN Health, a contract research organization that received research funding related to this study. Emma Merrill is a clinical research coordinator affiliated with MedStar Health. Nicholas Streicher and Farooq H. Sheikh are investigators affiliated with MedStar Health/Georgetown University School of Medicine, which received funding from Pfizer to support the research.

Ethical Approval. This study was approved by the MedStar Health Research Institute Institutional Review Board (IRB) (IRB ID: STUDY00006170) and granted a waiver from informed consent. The study followed Good Pharmacoepidemiology Practices guidelines and the principles of the Declaration of Helsinki.

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