Effects of Baseline Left Ventricular Hypertrophy and Decreased Renal Function on Cardiovascular and Renal Outcomes in Patients with Fabry Disease Treated with Agalsidase Alfa: A Fabry Outcome Survey Study

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ABSTRACT

Purpose: The initiation of enzyme-replacement therapy prior to the occurrence of substantial and irreversible organ damage in patients with Fabry disease is of critical importance. The Fabry Outcome Survey is an international disease registry of patients with a confirmed diagnosis of Fabry disease. In this study, data from the Fabry Outcome Survey were used for the assessment of the risks for cardiovascular and renal events in patients who received agalsidase alfa treatment.

Methods: Eligible patients were males and females aged ≥18 years with Fabry disease treated with agalsidase alfa. Cardiovascular events included myocardial infarction, left ventricular hypertrophy (LVH), heart failure, arrhythmia, conduction abnormality, and cardiac surgery. Renal events included dialysis, transplantation, and renal failure. Kaplan–Meier curves and log-rank tests were used for comparing event-free probabilities and time to first cardiovascular or renal event, from agalsidase alfa initiation to a maximum of 120 months, in patients with LVH versus normal left ventricular mass index (LVMI; ≤50 g/m².7 in males and ≤48 g/m².7 in females) at treatment initiation (baseline), and in patients with a low estimated glomerular filtration rate (eGFR; <90 mL/min/1.73 m²) versus normal eGFR at baseline. Multivariate Cox regression analysis was used for examining the association between key study variables and the risks for cardiovascular and renal events.

Findings: Among the 560 patients (269 males; 291 females) with available LVMI data, 306 (55%) had LVH and 254 (45%) had normal LVMI at baseline. The risk for a cardiovascular event was higher in the subgroup with LVH versus normal LVMI at baseline (hazard ratio [HR] = 1.57; 95% CI, 1.21–2.05; P < 0.001), but the risk for a renal event was similar between the 2 subgroups (HR = 1.90; 95% CI, 0.94–3.85; P = 0.074). Among the 1093 patients (551 males; 542 females) with available eGFR data, 433 (40%) had a low eGFR and 660 (60%) had a normal eGFR at baseline. The subgroup with a low eGFR at baseline had a significantly higher risk for a cardiovascular event (HR = 1.33; 95% CI, 1.04–1.70; P = 0.021) or a renal event (HR = 5.88; 95% CI, 2.73–12.68; P < 0.001) compared with patients with a normal eGFR at baseline.

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Implications: In the present study, the presence of LVH and/or reduced renal function at agalsidase alfa initiation was associated with a significantly higher risk for a cardiovascular or renal event, indicating that cardiovascular and renal pathologies in Fabry disease may be inter-related. Early initiation of agalsidase alfa treatment prior to the onset of severe organ damage may improve outcomes. ClinicalTrials.gov identifier: NCT03289065. (Clin Ther. xxxx;xxxxxx) © 2020 Takeda Pharmaceutical Company. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Key words: agalsidase alfa, enzyme-replacement therapy, estimated glomerular filtration rate, Fabry disease, Fabry Outcome Survey, left ventricular hypertrophy.

INTRODUCTION

Fabry disease is an X-linked genetic disorder in which deficient activity of the enzyme α-galactosidase A results in the progressive accumulation of glycosphingolipids in lysosomes. Multiple organ systems are affected, with cardiovascular and renal manifestations being important causes of morbidity and mortality.1

Enzyme-replacement therapy (ERT) with agalsidase alfa* or agalsidase beta† or the use of oral chaperone therapy, migalastat, in patients with an amenable mutation can improve symptoms and slow the progression of Fabry disease.2–5 However, it has become clear that the timing of treatment initiation in a more clearly defined patient cohort is an important factor influencing treatment efficacy. Starting ERT early in the disease course, before irreversible tissue changes and organ dysfunction occur, is recommended for an optimal therapeutic response.3,6–8 However, heterogeneity in the response to ERT suggests that the optimal timing of initiation is not always achieved.

The Fabry Outcome Survey (FOS), sponsored by Shire, a Takeda company, is an international registry of patients with a confirmed diagnosis of Fabry disease, in which longitudinal data have been collected for 19 years. Until 2016, patients were eligible for participation in FOS regardless of treatment with agalsidase alfa. Protocol amendment 4 (dated June 29, 2016) allowed all patients with Fabry disease, irrespective of treatment status with any approved therapy for Fabry disease, to be eligible for enrollment in FOS.

The present analysis of data from the FOS compared the risks for cardiovascular and renal events in agalsidase alfa ERT recipients who had left ventricular hypertrophy (LVH) and/or decreased renal function at baseline with those in patients with normal left ventricular mass index (LVMI) and/or normal renal function at treatment initiation.

PATIENTS AND METHODS

Patients

This was a retrospective analysis of data from the FOS (data extracted January 7, 2020; ClinicalTrials.gov identifier: NCT03289065). The FOS was approved by the institutional review boards of participating centers. This registry is compliant with relevant global and local regulations and best practices, including Good Pharmacoepidemiological Practice, Good Research for Comparative Effectiveness principles, and the relevant principles of the International Conference on Harmonisation Good Clinical Practice guidelines (E6) (see Supplemental Material in the online version at doi:10.1016/j.clinthera.2020.10.007). Patients were considered eligible for inclusion if they had initiated ERT with agalsidase alfa (0.2 mg/kg of body weight every 2 weeks) during adulthood (age of ≥18 years), had not experienced renal dialysis and/or kidney transplantation prior to agalsidase alfa start, and had undergone cardiovascular and/or renal assessments at the time of agalsidase alfa start. All participants or their caregivers provided written informed consent.

Outcomes

Cardiovascular events and markers of disease progression included myocardial infarction, LVH, heart failure, arrhythmia, conduction abnormality, and cardiac surgery. In patients who did not have LVH at baseline, the occurrence of any of the above-mentioned symptoms indicated that the patient experienced a cardiovascular event during the study.
follow-up period. In patients who had LVH at baseline, a cardiovascular event was defined as any of the above-mentioned symptoms (with the exception of LVH, which those patients had at baseline) experienced during the study follow-up period.

Renal events included reports of dialysis (hemodialysis, peritoneal, or unspecified), transplantation, and renal failure. Patients in whom renal dialysis and/or transplantation prior to agalsidase alfa initiation was reported were excluded. Left ventricular mass was calculated from linear septum, posterior wall, and cavity diameter, as measured by investigators using the Devereux-modified American Society of Echocardiography cube formula. LVMI was calculated by correcting left ventricular mass to height^{2.7.10,11} Estimated glomerular filtration rate (eGFR) was calculated by using the Chronic Kidney Disease Epidemiology Collaboration equation.12–14

Statistical Analysis
Initially, demographic and clinical characteristics of patients with normal and abnormal values of eGFR and LVMI at baseline were compared using the χ² test and the t test, as appropriate. Baseline value was defined as the measurement obtained on the date closest to agalsidase alfa initiation, within a window of −6 to +2 months. Kaplan–Meier curves and log-rank tests were used for comparing event-free probabilities and time to first cardiovascular or renal event from agalsidase alfa initiation up to 120 months of treatment in patients with LVH (LVMI >50 g/m^{2.7} in males; >48 g/m^{2.7} in females) versus normal LVMI (LVMI ≤50 g/m^{2.7} in males; ≤48 g/m^{2.7} in females) at baseline, and in patients with low eGFR (<90 mL/min/1.73 m^{2}) versus normal eGFR (≥90 mL/min/1.73 m^{2}) at baseline.10,11 Subsequently, multivariate Cox regression models were used for examining the association between key study parameters (sex, age, eGFR status, and LVMI status at agalsidase alfa initiation) and the risk for a cardiovascular and/or renal event. The level of statistical significance was set at 0.05. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS
Among the 560 patients with available baseline LVMI data, 306 (54.6%) had LVH and 254 (45.4%) had a normal LVMI. Of the 1093 patients with available baseline eGFR data, 433 (39.6%) had low eGFR and 660 (60.4%) were classified as having a normal eGFR value. Compared with the subgroup that had normal LVMI at baseline, the subgroup with LVH was similar in terms of sex distribution (47.7% vs 48.4% males; P = 0.867) but had a greater mean (SD) age at symptom onset (27.2 [18.7] vs 18.1 [15.4] years P < 0.001), age at diagnosis (45.2 [15.4] vs 30.4 [15.5] years P < 0.001), and age at agalsidase alfa start (51.2 [12.2] vs 37.0 [13.5] years P < 0.001), and lower eGFR (83.0 [24.7] vs 103.9 [22.3] mL/min/1.73 m² P < 0.001) (Table I).

Similarly, compared with the subgroup that had a normal eGFR at baseline, the subgroup with a low eGFR was of similar sex distribution (49.0% vs 51.4% males; P = 0.437) but had a greater mean (SD) age at symptom onset (28.7 [20.1] vs 21.0 [16.1] years P < 0.001), age at diagnosis (45.9 [16.8] vs 32.3 [15.5] years P < 0.001), and age at agalsidase alfa start (52.6 [12.9] vs 38.5 [13.2] years P < 0.001); and had a higher mean (SD) LVMI (60.8 [20.5] vs 49.0 [18.9] g/m^{2.7} P < 0.001).

The mean (SD) durations of treatment were similar between the subgroup with LVH versus the subgroup with a normal LVMI at baseline (6.9 [4.5] vs 7.6 [4.8] years, respectively P = 0.082), as well as between the subgroup of patients with low eGFR versus normal eGFR at baseline (6.8 [4.7] vs 6.4 [4.6] years P = 0.117). Event-free probabilities determined by Kaplan–Meier analysis and log-rank testing are presented in Figs. 1 and 2. The subgroup with LVH at baseline, compared with the subgroup with a normal LVMI at baseline, was at a significantly higher risk for a cardiovascular or renal event (P < 0.0001 and P = 0.0007, respectively; log-rank test) (Fig. 1).

The median times from agalsidase alfa initiation to first cardiovascular event were 9.6 and 53.4 months in the subgroups with LVH and normal LVMI at baseline, respectively (Table II). Regarding the median time to first renal event, this time was not reached, meaning that 50% of patients had not yet experienced a renal event at the end of the study follow-up period. The subgroup with a low eGFR at baseline had a significantly higher risk for a cardiovascular or renal event compared with the subgroup with normal eGFR at baseline (both, P < 0.0001; log-rank test) (Fig. 2). Moreover, this
| Characteristic                        | LVMI Abnormal | LVMI Normal | LVMI Total | P value | eGFR Abnormal | eGFR Normal | eGFR Total | P value |
|--------------------------------------|---------------|-------------|------------|---------|---------------|-------------|-------------|---------|
| Sex, n (%)                           |               |             |            |         |               |             |             |         |
| Female                               | 160 (52.3)    | 131 (51.6)  | 291 (52.0) | 0.867   | 221 (51.0)    | 321 (48.6)  | 542 (49.6)  | 0.437   |
| Male                                 | 146 (47.7)    | 123 (48.4)  | 269 (48.0) |         | 212 (49.0)    | 339 (51.4)  | 551 (50.4)  |         |
| Age at symptoms onset, years         |               |             |            | <0.001  | 28.7 (20.1)   | 21.0 (16.1) | 24.2 (18.2) | <0.001  |
| n                                    | 222           | 175         | 397        |         | 24.0 (10.0; 48.0) | 15.0 (8.0; 34.0) | 16.0 (9.0; 39.0) |       |
| Mean (SD)                            | 27.2 (18.7)   | 18.1 (15.4) | 23.2 (17.9) |         |               |             |             |         |
| Median (Q1; Q3)                      | 25.0 (10.0; 44.0) | 12.0 (7.0; 25.0) | 15.0 (8.0; 38.0) |         |               |             |             |         |
| Age at diagnosis, years              |               |             |            | <0.001  | 45.9 (16.8)   | 32.3 (15.5) | 37.8 (17.3) | <0.001  |
| n                                    | 303           | 248         | 551        |         | 48.0 (37.0; 58.0) | 31.0 (20.0; 43.0) | 38.0 (23.5; 52.0) |         |
| Mean (SD)                            | 45.2 (15.4)   | 30.4 (15.5) | 38.5 (17.1) |         |               |             |             |         |
| Median (Q1; Q3)                      | 46.0 (35.0; 56.0) | 27.0 (18.0; 41.0) | 40.0 (24.0; 52.0) |         |               |             |             |         |
| Age at agalsidase alfa initiation, years |               |             |            | <0.001  | 52.6 (12.9)   | 38.5 (13.2) | 44.1 (14.8) | <0.001  |
| n                                    | 306           | 254         | 560        |         | 53.2 (44.9; 61.7) | 36.9 (27.3; 47.9) | 44.4 (32.0; 55.5) |         |
| Mean (SD)                            | 51.2 (12.2)   | 37.0 (13.5) | 44.8 (14.6) |         |               |             |             |         |
| Median (Q1; Q3)                      | 50.9 (42.1; 61.0) | 34.2 (26.4; 46.7) | 45.2 (33.0; 56.4) |         |               |             |             |         |
| Duration of treatment, years         |               |             |            | 0.082   | 6.8 (4.7)     | 6.4 (4.6)   | 6.5 (4.6)   | 0.117   |
| n                                    | 306           | 254         | 560        |         | 5.7 (3.1; 9.9) | 5.0 (3.0; 8.5) | 5.2 (3.0; 9.2) |         |
| Mean (SD)                            | 6.9 (4.5)     | 7.6 (4.8)   | 7.2 (4.6)   |         |               |             |             |         |
| Median (Q1; Q3)                      | 6.0 (3.6; 9.3) | 7.1 (3.6; 11.5) | 6.3 (3.6; 10.1) |         |               |             |             |         |
| eGFR, mL/min/1.73m²                   |               |             |            | <0.001  | 66.1 (18.7)   | 112.6 (13.9) | 94.1 (27.8) | <0.001  |
| n                                    | 259           | 222         | 481        |         | 70.6 (54.5; 81.1) | 111.1 (100.7; 122.3) | 98.3 (76.4; 114.6) |         |
| Mean (SD)                            | 83.0 (24.7)   | 103.9 (22.3) | 92.7 (25.8) |         |               |             |             |         |
| Median (Q1; Q3)                      | 85.9 (67.7; 101.0) | 106.5 (88.6; 120.8) | 94.8 (76.9; 111.1) |         |               |             |             |         |
A group of patients had a significantly shorter time to first cardiovascular event (12.0 vs 69.2 months, respectively P < 0.001) (Table II). The median time from agalsidase alfa initiation to first renal event was not reached, meaning that 50% of patients had not yet experienced a renal event at the end of the study follow-up period.

The associations between key study parameters (ie, sex, age, eGFR, and LVMI at agalsidase alfa initiation) and the risk for a cardiovascular or renal event were investigated through multivariate Cox regression analyses (Table III). In accordance with the univariate findings of the log-rank testing, Cox regression revealed that a cardiovascular event was significantly more likely to occur in the subgroup with LVH and a low eGFR at agalsidase alfa initiation, whereas sex and age were not significantly associated. Specifically, compared with the subgroup without LVH at agalsidase alfa initiation, patients with LVH were 57% more likely to experience a cardiovascular event (hazard ratio [HR] = 1.57; 95% CI, 1.21–2.05; P < 0.001) (Table III). The subgroup with a low eGFR compared with the subgroup with a normal eGFR at agalsidase alfa initiation was 33% more likely to experience a cardiovascular event (HR = 1.33; 95% CI, 1.04–1.70; P = 0.021).

There were significant associations between male sex, LVH, and low eGFR at agalsidase alfa initiation and renal events. The subgroup with a low eGFR at agalsidase alfa initiation was 6-fold more likely to experience a renal event (HR = 5.88; 95% CI, 2.73–12.68; P < 0.001) (Table III), whereas in the subgroup with abnormal LVMI at agalsidase alfa initiation, the risk was almost 2-fold, but this difference was not statistically significant (HR = 1.90; 95% CI, 0.94–3.85; P = 0.074). Female sex was associated with a reduced risk for a renal event (HR = 0.27; 95% CI, 0.14–0.51; P < 0.001). However, age was not associated with the occurrence of a renal event (HR = 0.94; 95% CI, 0.73–1.20; P = 0.614).

DISCUSSION

In the present analysis in patients with confirmed Fabry disease who were treated with agalsidase alfa, the presence of LVH and reduced renal function at agalsidase alfa initiation were associated with significant risks for cardiovascular and renal events.
In support of these findings, Lenders et al\textsuperscript{15} reported that a low eGFR (≤75 mL/min/1.73 m\textsuperscript{2}) in ERT-naive patients with Fabry disease was associated with an increased risk for cardiovascular events, and an increased risk for combined cardiovascular, renal, and neurologic events, when on ERT. These observations were independent of sex. Arends et al\textsuperscript{16} reported that increasing age, male sex, and classic phenotype were predictive of clinical event rate and faster disease progression. After adjustment for these factors, they found that patients who had a lower eGFR at ERT initiation had an increased risk for a renal event, and that patients who had increased cardiac mass at baseline had a higher risk for a cardiovascular event.

Figure 1. Risk for a cardiovascular (A) or renal (B) event in agalsidase alfa—treated patients with Fabry disease and with normal or elevated left ventricular mass index (LVMI) at baseline. Abnormal is LVMI >50 g/m\textsuperscript{2}.7.

Figure 2. Risk for a cardiovascular (A) or renal (B) event in agalsidase alfa—treated patients with Fabry disease and with low versus normal estimated glomerular filtration rate (eGFR) at baseline. Abnormal is eGFR <90 mL/min/1.73 m\textsuperscript{2}.
cardiovascular event. The subgroups with LVH and a low eGFR had an older mean age at symptom onset or diagnosis compared with those with preserved LVMI and eGFR, consistent with a longer duration of the disease. However, it is notable that in the present analysis, age and sex were not associated with the risk for a cardiovascular event, whereas the risk for a renal event was found to be higher in males but was not associated with age. Nonetheless, the latter finding should be interpreted with caution, given the relatively low number of patients who experienced a renal event.

Chronic renal disease is a known risk factor for cardiovascular disease, and the results reported in the present analysis indicate a relationship between renal and cardiovascular pathologies in Fabry disease. Another study that investigated the impact of renal dysfunction on cardiovascular outcomes in Fabry disease reported that baseline cardiovascular parameters were worse in patients with end-stage renal disease than in those with mild renal disease. Furthermore, end-stage renal disease was strongly associated with progressive LVH.

Although the exact mechanisms leading to cardiovascular and renal impairment in Fabry disease are unclear, it may be that a similar pathophysiology is behind both. Fibrosis and inflammatory processes triggered by glycosphingolipid deposition and the possible subsequent release of secondary mediators of injury have been proposed as key contributors in organ damage in Fabry disease. Once the development of fibrosis has begun in tissues of the kidney and heart, ERT may not be as effective in preventing or slowing disease progression. The observations reported in the present analysis indirectly support the timely diagnosis of Fabry disease, before fibrosis or irreversible tissue changes occur, to facilitate early initiation of ERT and to help prevent progression toward poor cardiovascular and renal outcomes.

In addition, the pathogenic correlations between chronic kidney disease and myocardial disease are well known, in that LVH starts early in the process along with a mild reduction in GFR. Therefore, we can hypothesize that mechanisms such as LVH and vascular calcification are activated in patients with Fabry disease and nephropathy, and that they may play a role in determining a poorer prognosis, particularly in men with a severe classic phenotype of Fabry disease.

Observational studies, including analyses of data from patient registries, provide important evidence from clinical practice that complements the limited information available from randomized, controlled trials in rare diseases. However, with registry data in general, it is difficult to ensure comprehensive data capture; assessments may not be standardized across multiple sites, and there is the possibility of patient enrollment bias, as patients with more severe symptoms or who are receiving treatment are more likely to be enrolled in a registry. The patients enrolled in the FOS were not randomly selected, thus there was the potential for selection bias. Furthermore, because the present analysis included

| Event Type/Status   | No. of Patients | No. of Events | Median Time to First Event, mo |
|--------------------|----------------|--------------|-------------------------------|
| Cardiovascular LVMI|                |              |                               |
| Abnormal           | 306            | 223          | 9.6                           |
| Normal             | 254            | 142          | 53.4                          |
| eGFR               |                |              |                               |
| Abnormal           | 433            | 300          | 12.0                          |
| Normal             | 660            | 310          | 69.2                          |
| Renal LVMI         |                |              |                               |
| Abnormal           | 306            | 43           | Not reached                   |
| Normal             | 254            | 15           | Not reached                   |
| eGFR               |                |              |                               |
| Abnormal           | 433            | 90           | Not reached                   |
| Normal             | 660            | 23           | Not reached                   |

eGFR = estimated glomerular filtration rate; LVMI = left ventricular mass index.
*Baseline value defined as the measurement obtained on the date closest to agalsidase alfa initiation within −6 to +2 months.
†Defined as >50 g/m².⁷ in males, >48 g/m².⁷ in females.
‡Defined as <90 mL/min/1.73 m².
data from patients with impaired cardiovascular or renal status at baseline, it can be expected that cardiovascular and/or renal history will have some impact on cardiovascular and renal outcomes. Additionally, due to uncertainties with the calculation of eGFR, caution should be exercised when interpreting the eGFR data in this study. Although eGFR is widely used for classifying renal disease, age may influence eGFR, and the uncertainty of the eGFR calculation has led to overdiagnosis of some kidney disease. Lastly, the present study did not adjust for other variables (eg, proteinuria; arterial blood pressure; or the use of antihypertensive medications such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), which may have provided additional insights.

CONCLUSIONS
The findings from the present analysis suggest that cardiovascular and renal pathologies in Fabry disease are inter-related. These observations, in addition to those from previous studies, support the timely diagnosis of Fabry disease and the early initiation of ERT, before the onset of LVH or renal insufficiency, to prevent the pathologic processes that lead to poor cardiovascular and renal outcomes.

AUTHOR CONTRIBUTIONS
All of the authors made equal and substantial contributions to the interpretation of the data, drafting of the manuscript, revising it critically for important intellectual content, and final approval of the version to be submitted. V.K. made substantial contributions to the data analysis.

DATA AVAILABILITY
The datasets, including redacted study protocol, redacted statistical analysis plan, and individual participants’ data that composed the results reported in this article, will be available 3 months after the submission of requests to https://clinicaltrials.takeda.com/takedas-commitment?commitment=5 by researchers who provide a methodologically sound proposal after deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

DECLARATION OF COMPETING INTEREST
Shire International GmbH, a Takeda company, funded this research, its publication, and the writing and

| Event Type/Variable | Hazard Ratio (95% CI) | \(P\) |
|---------------------|----------------------|-------|
| **Cardiovascular event** | | |
| LVMI at baseline* (abnormal\(^1\) vs normal) | 1.57 (1.21–2.05) | <0.001 |
| eGFR at baseline* (abnormal\(^1\) vs normal) | 1.33 (1.04–1.70) | 0.021 |
| Sex (female vs male) | 0.92 (0.74–1.16) | 0.502 |
| Age at agalsidase alfa initiation (increment, +10 y) | 1.06 (0.96–1.16) | 0.264 |
| **Renal event** | | |
| LVMI at baseline* (abnormal\(^1\) vs normal) | 1.90 (0.94–3.85) | 0.074 |
| eGFR at baseline* (abnormal\(^1\) vs normal) | 5.88 (2.73–12.68) | <0.001 |
| Sex (female vs male) | 0.27 (0.14–0.51) | <0.001 |
| Age at agalsidase alfa initiation (increment, +10 y) | 0.94 (0.73–1.20) | 0.614 |

*Baseline value defined as the measurement obtained on the date closest to agalsidase alfa initiation, within –6 to +2 months.

\(^1\) Defined as >50 g/m\(^2.7\) in males, >48 g/m\(^2.7\) in females.

\(^2\) Defined as <90 mL/min/1.73 m\(^2\).

\(\text{CI} = \text{confidence interval; eGFR = estimated glomerular filtration rate; LVMI = left ventricular mass index.}\)
editing of the manuscript, and was involved in the study design; the collection, analysis, and interpretation of the data; the writing of the report; and the decision to submit the article for publication. The FOS is sponsored by Shire Human Genetic Therapies Inc. a Takeda company. Dr. Feriozzi reports personal and travel fees from Takeda, personal and travel fees from Sanofi, personal and travel fees from Amicus, outside the submitted work; Dr. Linhart reports grants and personal fees from Amicus Therapeutics, grants and personal fees from Sanofi Genzyme, grants and personal fees from Takeda, outside the submitted work; Dr. Gurevich was an employee of Takeda during the conduct of this study; Dr. Kalampoki was an employee of Takeda during the conduct of this study; Ms. Ramaswami reports personal fees from Chiesi, personal fees from Sano, reports grants and personal fees from Amicus, Takeda, personal fees from Idorsia, personal fees from Protalix, personal fees from Chiesi, personal fees from Sanofi Genzyme, grants from Takeda, outside the submitted work, and she is also a member of the Steering Committee of the Fabry Outcome Survey; Ms. Hughes was an employee of Takeda during the conduct of this study; Dr. Linhart reports grants and personal fees from Takeda, personal and travel fees from Chiesi, personal fees from Sano, reports grants and personal fees from Sanofi, personal fees from Chiesi, personal fees from Sanofi Genzyme, grants and personal fees from Takeda, outside the submitted work; Dr. Ramaswami reports grants and personal fees from Amicus, personal fees from Chiesi, personal fees from Sanofi Genzyme, grants from Takeda, personal fees from Idorsia, personal fees from Protalix, personal fees from Freeline, outside the submitted work, and she is also a member of the Steering Committee of the Fabry Outcome Survey.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinthera.2020.10.007.

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