FAbry STabilization indEX (FASTEX): an innovative tool for the assessment of clinical stabilization in Fabry disease

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Abstract

Two disease severity scoring systems, the Mainz Severity Score Index (MSSI) and Fabry Disease Severity Scoring System (DS3), have been validated for quantifying the disease burden of Fabry disease. We aimed to develop a dynamic mathematical model [the FASTEX (FAbry STabilization indEX)] to assess the clinical stability. A multidisciplinary panel of experts in Fabry disease first defined a novel score of severity [raw score (RS)] based on three domains with a small number items in each domain (nervous system domain: pain, cerebrovascular events; renal domain: proteinuria, glomerular filtration rate; cardiac domain: echocardiography parameters, electrocardiograph parameters and New York Heart Association class) and evaluated the clinical stability over time. The RS was tested in 28 patients (15 males, 13 females) with the classic form of Fabry disease. There was good statistical correlation between the newly established RS and a weighted score (WS), with DS3 and MSSI ($R^2 = 0.914, 0.949, 0.910$ and $0.938$, respectively). In order to refine the RS further, a WS, which was expressed as a percentage value, was calculated. This was based on the relative clinical significance of each item within the domain with the panel agreeing on the attribution of a different weight of clinical damage to a specific organ system. To test the variation of the clinical burden over time, the RS was repeated after 1 year. The panel agreed on a cut-off of a 20% change from baseline as the clinical WS to define clinical stability.

The FASTEX model showed good correlation with the clinical assessment and with clinical variation over time in all patients.
Introduction

Fabry disease is a lysosomal storage disorder caused by deficiency of the enzyme α-galactosidase A (αGal A) that is encoded by the GLA gene located on the X-chromosome locus Xq21.3-q22. This deficiency leads to the accumulation of glycosphingolipids, predominately globotriaosylceramide (GL-3) in various cell types and organs [1, 2], which causes a constellation of complications including skin lesions, peripheral neuropathy, stroke, arrhythmia, cardiomyopathy and renal failure [2]. Clinical signs and symptoms may be present in early childhood, and the earliest manifestations occurring in the classic form of Fabry disease include painful peripheral acropaesthesia and angiokeratoma [3]. With age, progressive damage to vital organs may lead to organ failure [2]. End-stage renal disease and life-threatening cardiovascular or cerebrovascular complications significantly reduce life expectancy [4, 5]. A ‘cardiac variant’ has been reported for patients with predominant or exclusive cardiac involvement [6, 7]. Female patients with Fabry disease may develop clinical signs ranging in intensity from being completely asymptomatic to severe disease similar to men with classic Fabry disease [8, 9]. This clinical variability is partly explained by the random X-chromosome inactivation (lyonization) [10]. Therefore, as for men with Fabry disease, assessing signs and symptoms of the disease in females and monitoring any clinical variation over time is mandatory [11]. Treatment of Fabry disease is based primarily on enzyme replacement therapy (ERT) with agalsidase alfa or agalsidase beta. Although ERT may be effective in halting disease progression when it is introduced at an early stage of the disease [12], it may not be able to stop disease progression when first administered in advanced stages. Therefore the ability to assess the degree of disease involvement and/or its stability is quite useful [13]. Two Fabry disease severity scoring systems, the Mainz Severity Score Index (MSSI) [14] and the Fabry Disease Severity Scoring System (DS3) [15], and a prognostic score index to predict natural history and prognosis of a single patient [16] have been previously validated. These tools provide an index of disease severity at a single time point, i.e. a snapshot of the clinical status of the individual patient, and do not allow evaluation of the clinical course over time. To date, there are no instruments that can demonstrate clinical stability, which represents an important goal in the management of patients with Fabry disease. Clinical stability of treated patients is indicative of the efficacy of ERT, and untreated patients who become clinically unstable may need to be initiated on treatment with ERT. However, to date there are no validated instruments that reliably assess clinical stability, which is a cornerstone of the management of patients with Fabry disease. Therefore we have developed a mathematical model [the Fabry STabilization indEx (FASTEX)] in order to objectively verify whether patients with Fabry disease remain clinically stable or become unstable over time.

Subject and methods applied to develop the raw score, weighted score and FASTEX

Consensus conference for raw score

During the first meeting in February 2014, relevant Fabry disease domains were identified using the Nominal Group Technique (NGT) of consensus formation [17]. The consensus defined a new score, the raw score (RS), based on 5-point Likert items [18] with three domains: nervous system, renal and cardiac. The domains contain the following items:

- Nervous system: pain, cerebrovascular events
- Renal: proteinuria and/or urinary albumin excretion, estimated glomerular filtration rate (eGFR)
- Cardiac: echocardiography parameters, electrocardiograph parameters, New York Heart Association (NYHA) class.

A scoring system ranging from 0 (no damage) to 4 (severe damage) was used for each of these seven items (Table 1).

The panel of experts involved in this project evaluated the RS jointly. Based on literature reviews [2, 14, 15, 19, 20] and personal routine clinical practice of following patients with Fabry disease, the panel reached a consensus on the hierarchy and score applied to each item and domain.

Consensus conference for weighted Score

During the second meeting in June 2014, a weighted score (WS) related to the clinical domains was discussed. The WS was proposed in order to capture the relative importance of progression from one RS to a higher score in each domain and it was derived from the RS according to the previously agreed hierarchy of clinical impact of organ involvement. It was expressed as a percentage of the maximum involvement score in each organ system (Table 2). Percentages of WS, as shown in Table 2, were approved by the panel members based on their personal clinical experience and articles/reviews published in the literature [2, 14, 15, 19, 20].

Consensus conference for clinical status

During the last meeting, held in October 2014, the panel analysed and reported the clinical status of the patients in the study using RSs and WSs. In addition, for each patient included in the study, the DS3 and MSSI scores were calculated. These four different scales used to calculate the clinical status of the patients were needed to verify and calculate the statistical correlation between RS, WS, DS3 and MSSI (Table 4). The demonstration of good statistical correlation with MSSI and DS3, which are two severity score systems already validated in the literature, was necessary to show that RS, and subsequently WS, are equally valid scoring systems, but utilizing a smaller number of variables that are also more objective and easier to assess, to evaluate disease severity. Since the FASTEX score is calculated from WS, which is based on RS, a good statistical correlation between RS, WS, MSSI and DS3 was required.

Application for RS, WS and Fastex

The aim of our study was to develop a mathematical model able to objectively verify whether patients with Fabry disease can be considered clinically stable or unstable during their clinical course.

A multidisciplinary panel of seven clinicians (cardiologists, nephrologists, neurologists, a paediatrician), all experts in the clinical management of Fabry disease, and two methodologist-
biostatisticians was established in 2014. A series of meetings were convened in order to study and develop a new mathematical model, the FASTEX.

To generate FASTEX, a new severity score system for Fabry disease had to be created. In order to be easily applicable in clinical practice, it needed to be a simpler, faster and more practical method to calculate disease severity than DS3 and MSSI.

Since the disease severity score in itself does not reflect either a clinical or an objective value of organ damage, we created a second score, the WS. The WS is an innovative new scoring system based on the individual items of the RS and is intended to reflect the degree of organ damage for each domain.

The concept of clinical stability depends on the variability of the condition of patients with Fabry disease over time. To reflect the spectrum of disease variability in patients with Fabry disease, we tested both the RS and WS in a population of 28 Fabry disease patients with different degrees of organ involvement at baseline (visit 1) and after 1 year (visit 2). The difference in the WS between the two clinical assessments resulted in the FASTEX score.

### Patient population

The patient population consisted of 28 Fabry disease patients [15 males (mean age 36 ± 18 years, range 8–65 years) and 13 females (mean age 47 ± 13 years, range 27–63 years)] with varying degrees of disease burden and followed at the authors’ centres. All patients enrolled in this study presented with the classic form of Fabry disease and a genotype associated with the classic disease pattern. The baseline (visit 1) analysis of the clinical condition of the patients is shown in Table 3.

### Statistical analysis

To assess long-term stability, the FASTEX takes into account, together with the RS, the status of the parameters at two different temporal points. Through the allocation of their respective weights, these scores are converted into percentages (WS; Table 2). The scores are reported in a graph where, for each parameter, it is possible to determine the extent of worsening/improvement during the time interval between two visits. The overall stability of the disease is obtained from the sum of worsening or improving scores.

The severity of each domain was calculated using the root mean square (RMS) of the respective items related to

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**Table 1. Raw score: nervous, renal and cardiac systems**

<table>
<thead>
<tr>
<th>Score</th>
<th>Nervous system score</th>
<th>Renal system score</th>
<th>Cardiac system score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Score</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Events</td>
<td>Score</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>ACR/PCR</td>
<td>Score</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>LVH</td>
<td>Score</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>ECG/arrhythmia</td>
<td>Score</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>NYHA</td>
<td>Score</td>
<td>0</td>
<td>40</td>
</tr>
</tbody>
</table>

**Table 2. Weighted score expressed as a percentage of organ damage**

<table>
<thead>
<tr>
<th>Nervous system score</th>
<th>Renal system score</th>
<th>Cardiac system score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain %</td>
<td>Score</td>
<td>0</td>
</tr>
<tr>
<td>Events %</td>
<td>Score</td>
<td>0</td>
</tr>
<tr>
<td>ACR/PCR %</td>
<td>Score</td>
<td>0</td>
</tr>
<tr>
<td>eGFR %</td>
<td>Score</td>
<td>0</td>
</tr>
<tr>
<td>LVH %</td>
<td>Score</td>
<td>0</td>
</tr>
<tr>
<td>ECG/arrhythmia %</td>
<td>Score</td>
<td>0</td>
</tr>
<tr>
<td>NYHA %</td>
<td>Score</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 3. Clinical involvement at baseline (visit 1)**

<table>
<thead>
<tr>
<th>Involvement</th>
<th>Patient#</th>
<th>Nervous system</th>
<th>Renal</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single organ</td>
<td>6</td>
<td>3</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Two organs*</td>
<td>7</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Multiple organs</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>No organ damage</td>
<td>5</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>On ERT at baseline</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Three cases had nervous system and renal involvement; four cases had cardiac and renal involvement.

**Patient population**

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**Statistical analysis**

To assess long-term stability, the FASTEX takes into account, together with the RS, the status of the parameters at two different temporal points. Through the allocation of their respective weights, these scores are converted into percentages (WS; Table 2). The scores are reported in a graph where, for each parameter, it is possible to determine the extent of worsening/improvement during the time interval between two visits. The overall stability of the disease is obtained from the sum of worsening or improving scores.

The severity of each domain was calculated using the root mean square (RMS) of the respective items related to
that domain expressed as a percentage. The RMS method enables distinguishing the result of equal sums obtained from components with different values. By using RMS, it is possible to calculate any combination of scores for any potential hypothetical patient and for all domains (Supplementary data).

The overall severity of the disease, reported as a percentage, was calculated as the sum of each severity domain corrected by their interaction, as shown in the following algorithm:

\[ 100 \times (A + (1 - A) \times B + (1 - (A + (1 - A) \times B)) \times C). \] (1)

which simplifies to:

\[ 100 \times (A + B + C + A \times B + C - A \times B - A \times C - B - C). \] (2)

where A = RMS of the nervous system domain, B = RMS of the renal domain and C = RMS of the cardiac domain.

Using this algorithm, we ascertain that if there is only one compromised domain, the patient's total disease severity equals the value of this domain. Finally, if the severity of each domain is lower than the maximum severity (100%), the formula provides an higher result proportional to the severity of the most severely affected domain (Figure 1).

All combinations of scores for each domain system (nervous, renal and cardiac) calculated by applying the algorithm specified above are provided in the Supplementary data. These values represent all possible combinations of percentages for organ damage subdivided for each domain (Figures 2 and 3).

Results
Coefficient of correlation between RS, WS, DS3 and MSSI

Coefficients of correlation \( (r^2) \) between the different scoring systems were good (Table 4), even with the relatively small sample size. This finding is in line with the fact that the new scores were developed based on previously published scores [14, 15]. However, our new model is faster and easier to use. To test the adherence with the previously published disease severity indices, a specific coefficient of correlation was calculated between RS, WS, DS3 and MSSI, as shown in Table 4.

Clinical stability

The working group reached a consensus on a score (FASTEX) to be able to determine when a patient can be considered stable or unstable. Following this method and applying this concept to the algorithm, any worsening with a global score \( \geq 20\% \) suggests that the patient is clinically unstable, regardless of the result of the sum of the improvement scores. It is important to underline that the interpretation becomes more problematic when, in the same patient, there is evidence of improvement in some parameters but worsening in other parameters. Since quantifying the balance between improvement and worsening is very difficult from a statistical point of view, the working panel reviewed the clinical variation between visits and agreed that a variation in the clinical status of the FASTEX score \( \geq 20\% \) is an unstable clinical condition while a score of \( <20\% \) corresponds to a stable clinical condition.

Illustrative cases of clinically stable and unstable patients are provided below

Example 1 – Patient not stable (atrial fibrillation present at the second visit while no cardiac abnormality was present at baseline) (Table 5).

\[ WS = \frac{Weighed\ Score}{RS} = \frac{Raw\ Score}{1} \]

- Change in the severity score of the cardiac domain: ECG/arrhythmia from 0 to 45%;
- FASTEX = 45% (>20%)

Example 2 – Patient stable despite mild clinical worsening: the patient refers the onset of pain at the extremities and there is mild hyperfiltration at the second visit as compared to baseline, but the FASTEX is <20% (Table 6).

\[ WS (RS) = Weighed\ Score (Raw\ Score) \]

- Change in nervous system domain: pain from 0 to 5%;
- Change in renal domain: eGFR from 0 to 10% (20%);
- FASTEX = 15% (<20%)

Example 3 – Patient not stable despite some clinical improvement: after visit 1, when the patient started ERT; at the second visit, pain becomes mild but renal function shows hyperfiltration and a short PR interval is present on the ECG (Table 7).

\[ WS (RS) = Weighed\ Score (Raw\ Score) \]

- Change in nervous system domain: pain from 20 to 5% (−15%);
- Change in renal domain: eGFR from 0 to 10% (+10%);
- Change in cardiac domain: EKG/arrhythmia from 0 to 25% (+25%);
- FASTEX = +35% (>20%)

Discussion

To date, two severity scoring systems (MSSI and DS3) to quantify the disease burden in Fabry disease have been validated [14, 15]. Both of these require evaluation of several domains with a large number of items (5 domains and 12 items for DS3 and 4 domains and 24 items for MSSI) resulting in a time-consuming and potentially difficult calculation and application of the indices. In addition, some items of these indices are based largely on patients’ self-reported evaluation of symptoms. Furthermore, these scoring systems only permit static snapshots of the clinical status of the patient at the time of the visit without providing an estimation of the clinical variation as compared with previous visits.

Although the concept of disease stabilization is an important therapeutic goal in the management of Fabry disease, there are currently no easy and reliable tools available to define and measure stability without performing biopsies to quantify GL-3 accumulation in capillary endothelial cells, renal cells (podocytes, tubular cells, glomerular endothelial, mesangial and interstitial cells), cardiac cells (cardiomyocytes and fibroblasts) and the cells of the peripheral, autonomic and central nervous systems [2].

Fabry disease is a progressive disease and periodic evaluation of the clinical status is mandatory. A worldwide consensus on the exact timing for starting ERT and whether it should be stopped in the later stages of the disease has not yet been established. Recent reports suggest starting ERT at the time of the diagnosis in males and in symptomatic females, while in asymptomatic females the current opinion is to monitor the patient and start ERT at the onset of signs or symptoms of the disease [19]. Periodic evaluation allows for early detection of disease progression in asymptomatic patients not yet receiving ERT and to assess disease stability or progression, particularly in patients with...
advanced organ involvement at baseline. Both ERT and adjunctive therapies are directed at relieving symptoms, protecting organs and arresting disease progression.

The aim of our study was to develop an index of stability/change of state for monitoring of patients with Fabry disease. First, we generated a new severity score, the RS, based on only

Fig. 1. (A) Percentage severity of single domains and total severity score. (B) Total percentages of severity for single domains and total severity score at first and second visit calculated by applying the algorithm.
three domains and seven items. As compared with the DS3 and MSSI indexes, our scoring method is simpler, more practical and faster to calculate and therefore easier to apply in clinical practice.

To take into account the relative importance of each of the items, we then introduced the WS. Both the RS and WS were statistically correlated with the MSSI and DS3, showing that the same accuracy can be obtained by including a smaller number of items.

Fig. 2. (A) Percentage severity of single domains and total severity score. (B) Total percentages of severity for single domains and total severity score at first and second visit calculated by applying the algorithm.
in the calculation of the score. The proposed scores are also likely to be more objective because a number of items in the MSSI and DS3, e.g. pain intensity, are dependent on a subjective evaluation by the patient. Moreover, no differences in the clinical presentation between the new index (FASTEX) and the two validated models (DS3 and MSSI) have been observed. The main innovation,
when compared with the DS3 and MSSI, is the introduction of an overall score taking into account the scores of single organs. Since the concept of stability depends on the variation of the clinical condition of patients with Fabry disease over time, we applied and calculated both RS and WS in a population of 28 Fabry disease patients with different degrees of organ involvement at baseline (visit 1) and after 1 year (visit 2). The difference in the WS between the two clinical assessments resulted in the FASTEX score. After evaluation of the clinical variation between visits 1 and 2 of all patients in the study, the working panel reviewed the results and agreed to consider a FASTEX score ≥20% as indicative of clinically significant deterioration of the patient’s disease, while a score of <20% corresponds to stability or improvement of the clinical condition. A FASTEX score of 20% is therefore to be considered as the threshold limit of stability. A detailed analysis of the follow-up of each patient between visit 1 and 2 confirms that the FASTEX score in each patient correlates with the follow-up of all the patients enrolled in the study. In other words, patients with a FASTEX score of <20% do not have any clinical variation, or at most a small clinical variation at the second visit as compared with the baseline. Patients with a FASTEX score >20% have a significant clinical deterioration during the follow-up period. Even though the onset of only one new sign or symptom in a stable patient is indicative of a clinical variation per se, the FASTEX model allows quantification of the variation in the same patient over time. In untreated female patients, the onset of any sign or symptom of the disease with a FASTEX score >20% may reflect disease progression and warrants therapeutic intervention, i.e. starting ERT. In all other patients already treated with ERT, worsening of the FASTEX score could lead to a re-evaluation of the therapy with a potential adjustment of the dose of ERT and/or to the modification of supportive therapy.

A limitation of this new FASTEX model concerns the specific population of Fabry patients included in the study to test the model. These patients were routinely monitored at the panel members’ medical institutes. FASTEX needs to be further validated in patient populations from other centres. More comprehensive data from a larger population may allow further guidance on how changes over time should be interpreted, particularly in combination with emerging biomarkers, e.g. globotriaosylsphingosine (lyso-GL-3), which is being studied for its utility in the diagnosis and follow-up of Fabry disease. Explanation of how the algorithm was built to calculate the overall severity of patients is provided in Supplementary data. To avoid the need to use complex spreadsheet programs, the authors are currently preparing a free app in order to facilitate wider use of the FASTEX. This app is intended to be very user friendly: the operator will need to provide the RS index based on the clinical and laboratory exams and the app will automatically calculate WS and subsequently the FASTEX index after the second visit.

### Conclusions

In summary, a new consensus-based and simpler disease severity score is proposed that may allow quick and easy estimation of disease stability or progression. The FASTEX should be applied by clinicians from different international groups to confirm the accuracy and value of this new clinical tool that may contribute to better clinical assessment and management of patients with Fabry disease. Since this score needs to be validated in a wider cohort, full validation will require more extensive retrospective and prospective studies in different populations of patients with Fabry disease.

### Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

### Acknowledgements

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### Table 4. Coefficient of correlation ($r^2$) between RS, WS, DS3 and MSSI

<table>
<thead>
<tr>
<th></th>
<th>RS</th>
<th>WS</th>
<th>DS3</th>
<th>MSSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r^2$</td>
<td>1.000</td>
<td>0.995</td>
<td>0.914</td>
<td>0.494</td>
</tr>
</tbody>
</table>

### Table 5. Clinical parameters based on WS and RS values

<table>
<thead>
<tr>
<th>Nervous system</th>
<th>Renal</th>
<th>Cardiac</th>
<th>ECG/arrhythmia</th>
<th>NYHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Events</td>
<td>ACR/PCR</td>
<td>eGFR</td>
<td>LVH</td>
<td></td>
</tr>
<tr>
<td>1st visit</td>
<td>5 (1)  0 (0)</td>
<td>0 (0)  50 (2)</td>
<td>10 (1)  0 (0)</td>
<td>40 (1)</td>
</tr>
<tr>
<td>2nd visit</td>
<td>5 (1)  0 (0)</td>
<td>0 (0)  50 (2)</td>
<td>10 (1)  45 (2)</td>
<td>40 (1)</td>
</tr>
</tbody>
</table>

Values are presented as WS (RS). ACR, urinary albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; ECG, electrocardiogram; PCR, urinary protein:creatinine ratio.

### Table 6. Clinical parameters based on WS and RS values

<table>
<thead>
<tr>
<th>Nervous system</th>
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<th>Cardiac</th>
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<tbody>
<tr>
<td>Pain Events</td>
<td>ACR/PCR</td>
<td>eGFR</td>
<td>LVH</td>
<td></td>
</tr>
<tr>
<td>1st visit</td>
<td>0 (0)  0 (0)</td>
<td>0 (0)  0 (0)</td>
<td>0 (0)  45 (2)</td>
<td>40 (1)</td>
</tr>
<tr>
<td>2nd visit</td>
<td>5 (1)  0 (0)</td>
<td>0 (0)  10 (1)</td>
<td>0 (0)  45 (2)</td>
<td>40 (1)</td>
</tr>
</tbody>
</table>

Values are presented as WS (RS). ACR, urinary albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; ECG, electrocardiogram; PCR, urinary protein:creatinine ratio; NYHA, New York Heart Association class; PCR, urinary protein:creatinine ratio.

### Table 7. Clinical parameters based on WS and RS values

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<th>Cardiac</th>
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<tbody>
<tr>
<td>Pain Events</td>
<td>ACR/PCR</td>
<td>eGFR</td>
<td>LVH</td>
<td></td>
</tr>
<tr>
<td>1st visit</td>
<td>20 (2)  10 (1)</td>
<td>0 (0)  10 (1)</td>
<td>0 (0)  40 (1)</td>
<td></td>
</tr>
<tr>
<td>2nd visit</td>
<td>5 (1)  10 (1)</td>
<td>0 (0)  10 (1)</td>
<td>10 (1)  25 (1)</td>
<td>40 (1)</td>
</tr>
</tbody>
</table>

Values are presented as WS (RS). ACR, urinary albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; ECG, electrocardiogram; PCR, urinary protein:creatinine ratio; NYHA, New York Heart Association class; PCR, urinary protein:creatinine ratio.
discussion meetings and writing and submission of the article. However, the company had no direct involvement in the collection, analysis and interpretation of data, in the writing of the article, in the decision to submit the manuscript for publication and in the selection of the targeted journal. The authors declare that all procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients included in the study.

Conflicts of interest statement

R.M. declares that he has received fees from Sanofi Genzyme during the conduct of the study, grants and personal fees from SHIRE and grants and personal fees from Sanofi Genzyme outside the submitted work. F.P. declares that he has received fees from Sanofi Genzyme during the conduct of the study, grants and personal fees from Sanofi Genzyme Company outside the submitted work. F.B. declares that he has no conflict of interest. M.G. declares that he has received speaking honoraria and travel grants from Genzyme and personal fees from Sano oraria and travel grants from Genzyme and personal fees from Sano and grants and personal fees from SHIRE and grants and personal fees from Sano Genzyme Company outside the submitted work. M.S. declares that he has received speaking honoraria from Genzyme during the conduct of the study and personal fees from Genzyme and grants and personal fees from Sano Genzyme Company outside the submitted work. M.P. declares that he has received fees from Sano Genzyme during the conduct of the study, grants and personal fees from Sanofi Genzyme Company outside the submitted work. F.P. declares that he has received fees from Sanofi Genzyme during the conduct of the study and personal fees from Sanofi Genzyme. M.S. declares that he has received speaking honoraria and travel grants from Genzyme and personal fees from Sano Genzyme during the conduct of the study. A.B. declares that she has received fees from Sano Genzyme during the conduct of the study and personal fees from Sanofi Genzyme during the conduct of the study. A.S. declares that he has received speaking honoraria and travel grants from Genzyme and personal fees from Sanofi Genzyme during the conduct of the study and personal fees from Sanofi Genzyme. M.G. declares that he has received speaking honoraria and travel grants from Genzyme and personal fees from Sano Genzyme during the conduct of the study. A.B. declares that she has received fees from Sano Genzyme during the conduct of the study, grants and personal fees from Sanofi Genzyme Company outside the submitted work. F.B. declares that he has no conflict of interest. A.B. declares that he has received speaking honoraria and travel grants from Genzyme and grants as a member of the advisory board of the European Fabry Registry from Genzyme. B.C. declares that he has no conflict of interest. M.G. declares that he has received speaking honoraria and travel grants from Genzyme and grants and personal fees from Sanofi Genzyme Company outside the submitted work. M.S. declares that he has received speaking honoraria and travel grants from Genzyme, personal fees from Sanofi Genzyme during the conduct of the study and personal fees from Sanofi Genzyme outside the submitted work.

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