

# Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease

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## Abstract

### Objective

To determine the effects of 10 years of enzyme replacement therapy (ERT) in adult patients with Pompe disease, focusing on individual variability in treatment response.

### Methods

In this prospective, multicenter cohort study, we studied 30 patients from the Netherlands and France who had started ERT during the only randomized placebo-controlled clinical trial with ERT in late-onset Pompe disease (NCT00158600) or its extension (NCT00455195) in 2005 to 2008. Main outcomes were walking ability (6-minute walk test [6MWT]), muscle strength (manual muscle testing using Medical Research Council [MRC] grading), and pulmonary function (forced vital capacity [FVC] in the upright and supine positions), assessed at 3- to 6-month intervals before and after the start of ERT. Data were analyzed with linear mixed-effects models for repeated measurements.

### Results

Median follow-up duration on ERT was 9.8 years (interquartile range [IQR] 8.3–10.2 years). At the group level, baseline 6MWT was 49% of predicted (IQR 41%–60%) and had deteriorated by 22.2 percentage points (pp) at the 10-year treatment point ( $p < 0.001$ ). Baseline FVC upright was 54% of predicted (IQR 47%–68%) and decreased by 11 pp over 10 years ( $p < 0.001$ ). Effects of ERT on MRC sum score and FVC supine were similar. At the individual level, 93% of patients had initial benefit of ERT. Depending on the outcome measured, 35% to 63% of patients had a secondary decline after  $\approx 3$  to 5 years. Still, at 10 years of ERT, 52% had equal or better 6MWT and/or FVC upright compared to baseline.

### Conclusions

The majority of patients with Pompe disease benefit from long-term ERT, but many patients experience some secondary decline after  $\approx 3$  to 5 years. Individual variation, however, is considerable.

### Classification of evidence

This study provides Class IV evidence that for the majority of adults with Pompe disease, long-term ERT positively affects, or slows deterioration in, muscle strength, walking ability, and/or pulmonary function.

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## Glossary

**ERT** = enzyme replacement therapy; **FVC** = forced vital capacity; **IQR** = interquartile range; **LOTS** = Late-Onset Treatment Study; **MEP** = maximal expiratory pressure; **MIP** = maximal inspiratory pressure; **MRC** = Medical Research Council; **M6P** = mannose-6-phosphate; **pp** = percentage points; **QMT** = quantitative muscle testing; **6MWT** = 6-minute walk test.

Enzyme replacement therapy (ERT) with recombinant human acid  $\alpha$ -glucosidase (alglucosidase alfa, myozyme) has become the standard of care in the treatment of patients with Pompe disease, a relentlessly progressive, autosomal recessive myopathy caused by a deficiency of acid  $\alpha$ -glucosidase.<sup>1,2</sup> The disease may manifest at any age, from infancy to late adulthood, and the type and severity of symptoms vary widely. Skeletal muscle weakness and respiratory dysfunction are the hallmarks of the phenotype in adults.<sup>3,4</sup> Ultimately, without treatment, the majority of adult patients become dependent on the use of a wheelchair and/or mechanical ventilatory support, leading to severe limitations in daily living.

Several longitudinal studies up to a median of 5 years of ERT treatment showed that treated patients had improved ambulatory function and muscle strength, stabilization of pulmonary function, and increased survival.<sup>5–10</sup> However, recent studies show that the effect of ERT seems to peak at 2 to 3 years of treatment and is followed by a plateau or secondary decline. Because no studies with follow-up >5 years are available, it is unknown if this plateau is maintained or whether a further, more rapid, decline follows. Furthermore, several studies have reported substantial individual differences in treatment benefit.<sup>6,8,9</sup> A better understanding of such differences could help to predict individual treatment response and to guide decisions about starting and stopping ERT.

We had the unique opportunity to study 30 patients from the Netherlands and France who had participated in the only randomized placebo-controlled clinical trial with ERT in late-onset Pompe disease<sup>11,12</sup> who have now been carefully followed up for 10 years. We investigated the effects of ERT on muscle strength, walking ability, and pulmonary function and delineated individual patients' treatment response.

## Methods

### Study design and participants

This study was a prospective, open-label cohort study involving 30 patients with a confirmed diagnosis of Pompe disease. It is being conducted at the Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam (n = 20), and the Institute of Myology, Pitié-Salpêtrière Hospital, Paris (n = 10), both nationally endorsed centers of expertise in Pompe disease. From 2005 to 2007, all patients had participated in the randomized, double-blind, placebo-controlled study on the effects of enzyme therapy in patients with late-onset Pompe (Late-Onset Treatment

Study [LOTS], NCT00158600),<sup>11</sup> in which patients were randomized in a 2:1 ratio to receive biweekly IV infusions of 20 mg/kg alglucosidase alfa or placebo for up to 78 weeks. Eligibility criteria for that study included (1) evidence of lower extremity muscle weakness while still being able to walk 40 m on the 6-minute walk test (6MWT); (2) an upright seated forced vital capacity (FVC) percent predicted between 30% and 80%; (3) a drop in FVC of  $\geq 10\%$  when changing from the upright to the supine position; (4) no invasive ventilation; and (5) no noninvasive ventilation while awake and upright. In the subsequent open-label extension study (NCT00455195), all patients received alglucosidase alfa for another 26 weeks.<sup>12</sup> ERT was continued thereafter unless patients experienced unmanageable adverse reactions or decided to stop treatment. Clinical assessments took place every 3 to 6 months before and after the start of ERT. The earliest measurements before the start of ERT that were used to assess the disease course of untreated patients are from 1991. For this study, database lock was July 1, 2016.

## Procedures

### Walking ability and muscle strength

We used the 6MWT as a test of functional endurance. Values are presented as a percentage of predicted normal values to account for the effects of age, height, weight, and sex.<sup>13</sup>

In addition, skeletal muscle strength was measured by manual muscle testing with the Medical Research Council (MRC) grading scale<sup>14</sup> or the modified MRC scale.<sup>15</sup> For the purpose of the current analyses, only full grades (0–5) were used. The following muscle groups were tested to calculate an MRC sum score (range 0–95): neck flexors, bilateral shoulder abductors, elbow flexors, elbow extensors, hip flexors, hip extensors, hip abductors, hip adductors, knee flexors, and knee extensors. This score was subsequently converted to a percentage of the maximum possible score. As an additional outcome of muscle strength, we used the quantitative measurement system (quantitative muscle testing [QMT]) of the Cooperative International Neuromuscular Research Group (maximal voluntary isometric contraction) to calculate a composite QMT leg score.<sup>11,16,17</sup>

### Pulmonary function

FVC was measured with the patient in an upright seated and a supine position. Furthermore, maximal inspiratory (MIP) and maximal expiratory (MEP) mouth pressures were measured in the upright seated position. All measurements were performed according to standards of the American Thoracic Society/European Respiratory Society.<sup>18,19</sup>

Results were expressed as a percentage of the predicted normal value.<sup>20,21</sup>

### Additional clinical information

Information was gathered on the following: (1) sex; (2) height; (3) weight; (4) age at symptom onset; (5) age at the start of ERT, (6) use of a wheelchair; (7) use of mechanical ventilatory support; (8) genotype; and (9) peak titers of antibodies against alglucosidase alfa during the first 3 years of ERT.<sup>11,22,23</sup>

## Statistical analyses

### Group level

Longitudinal analyses of 6MWT, MRC sum score, QMT leg score, FVC upright, FVC supine, MIP, and MEP were performed with linear mixed models to account for correlations in the repeated measurements per patient, as reported previously.<sup>8</sup> The current analyses include between 503 and 604 measurements per outcome measure. Measurements performed after cessation of ERT treatment were excluded. We report the outcomes at 10 years of treatment compared to baseline. To correct for possible differences between the patients at the start of ERT and how these may affect the longitudinal profiles of the outcome, we included interactions of the nonlinear time effect with sex, disease duration at the start of ERT ( $\leq 17$  or  $> 17$  years; calculated from onset of first symptoms), FVC upright at the start of ERT ( $\leq 55\%$  or  $> 55\%$  predicted), and 6MWT at the start of ERT ( $\leq 50\%$  or  $> 50\%$  predicted) in the models. Cutoff points are based on median values of the total group. These interactions were retained if they were found to improve the fit of the model. The assumptions of the models were checked with residual plots.

For FVC, sufficient data on the disease course before start of ERT (i.e., natural disease course) were available to compare patients' outcomes under treatment with their situation without treatment. To this end, we extrapolated patients' natural course data, assuming linear evolutions over time,<sup>8,24</sup> and compared these to the observed values at the 10-year treatment point. We used all data until the time point at which 95% of data were available to avoid influence of individual patients with longer follow-up.

Overall treatment effects were tested with likelihood ratio tests. Differences were expressed in absolute percentage points (pp). The significance level was set at 0.05.

### Individual level

For 6MWT, MRC sum score, QMT leg score, FVC upright, and FVC supine, we assessed patients' individual response to ERT until cessation of treatment or end of follow-up, respective to their situation at the start of ERT. Per outcome, each patients' course during ERT was visualized in scatterplots. Subsequently, 5 independent observers (clinicians involved in the care for patients with Pompe disease) blinded

for the patient's identification classified their response into 8 groups: (1) improvement throughout the study; (2) initial improvement followed by stabilization; (3) initial improvement followed by decline; (4) stable throughout the study; (5) initial stabilization followed by decline; (6) decline throughout the study; (7) initial decline followed by stabilization or improvement; and (8) unclassifiable. Examples of the various response patterns are shown in figure 1. Consensus was reached when at least 4 of the observers agreed on the response pattern. If no consensus had been reached, results were discussed in a separate meeting (L.H., J.-Y.H., N.A.M.E.v.d.B.). For more intuitional interpretation of the overall results, initial improvement or stabilization with regard to a patient's baseline measurement was classified as a positive response, even if followed by a secondary decline later during follow-up (figure 1, patterns 1 through 5), while deterioration despite ERT was regarded as a negative outcome (figure 1, pattern 6).

In addition, we assessed patients' individual response to ERT respective to the start of treatment. Their response was classified into 3 groups: improvement ( $> 2$  pp above baseline level), stabilization (between  $-2$  and  $+2$  pp from baseline level), and deterioration ( $> 2$  pp below baseline level).

Analyses were performed with SPSS for Windows (version 24, SPSS Inc, Chicago, IL) and R version 3.2.2 (2015-08-14, R Foundation for Statistical Computing, Vienna, Austria) using the nlme package (version 3.1-121).

## Standard protocol approvals, registrations, and patient consents

The study protocols were approved by the Medical Ethical Committees of Erasmus MC University Medical Center or Pitié-Salpêtrière Hospital. All patients gave their written informed consent.

## Classification of evidence

This study provides Class IV evidence that for the majority of adults with Pompe disease, long-term ERT positively affects, or slows deterioration in, muscle strength, walking ability, and/or pulmonary function.

## Data availability

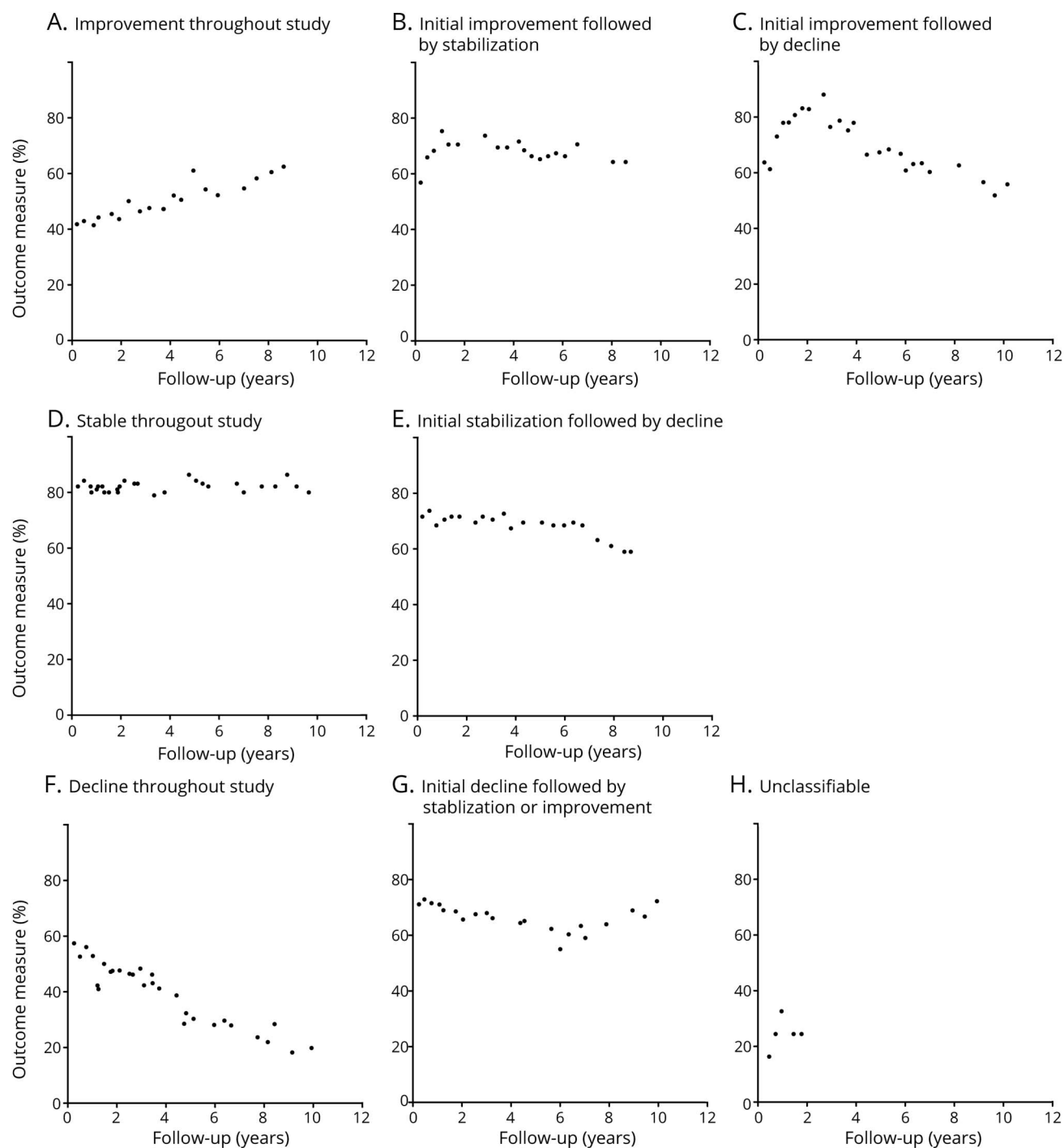
Anonymized data will be shared by request from any qualified investigator for the sole purpose of replicating procedures and results presented in the article and as long as data transfer is in agreement with European Union legislation on the general data protection regulation.

# Results

## Patients

Thirty patients (the Netherlands  $n = 20$ , France  $n = 10$ ) participated in this study (table). There were no differences in age, disease duration, or disease severity at the start of ERT

**Figure 1** Definition of response patterns



Individual response to enzyme replacement therapy was classified into 1 of 8 different response patterns defined: (A) improvement throughout the study, (B) initial improvement followed by stabilization, (C) initial improvement followed by decline, (D) stable throughout the study, (E) initial stabilization followed by decline, (F) decline throughout the study, (G) initial decline followed by stabilization or improvement, and (H) unclassifiable.

between the Dutch and French patients. Median overall follow-up on ERT was 9.8 years (interquartile range [IQR] 8.3–10.2 years). At the start of ERT, the median age was 49 years (IQR 41–60 years), and the median disease duration from symptom onset was 17 years (IQR 10–23 years). Figure 2 shows the clinical course of the individual patients over time, including age at first symptoms, age at the start of

ERT, age at the start of using a wheelchair and/or ventilation, and, if applicable, age at death.

### Group level

#### Walking ability and muscle strength

At the start of ERT, the median distance walked on the 6MWT was 49% of predicted (IQR 41%–62%) (table).

**Table** Patients' characteristics

<b>Patients, n (% of total)</b>	30 (100)	
<b>Male</b>	14 (47)	
<b>Female</b>	16 (53)	
<b>Genotype, n (% of total) (n = 30)</b>		
c.-32-13T>G/c.525delT	9 (30)	
c.-32-13T>G/other disease-causing variant <sup>a</sup>	19 (63)	
c.1748C>T/c.2014C>T	2 (7)	
<b>Peak titers of antibodies against alglucosidase alfa,<sup>b</sup> n (% of total) (n = 30)</b>		
<b>Low (0-&lt;1:1,250)</b>	4 (13)	
<b>Intermediate (1:1,250-&lt;1:31,250)</b>	16 (53)	
<b>High (≥1:31,250)</b>	9 (30)	
<b>Not available</b>	1 (3)	
<b>Patients stopped ERT, n (% of total) (n = 30)</b>	3 (10)	
<b>Patients died during treatment with ERT, n (% of total) (n = 30)</b>	1 (3)	
<b>Follow-up duration on ERT, median (IQR), y</b>	9.8 (8.3–10.2)	
<b>Baseline characteristics at start of ERT, median (IQR)</b>		
<b>Age, y</b>	49 (41–60)	
<b>Disease duration from symptom onset, y</b>	17 (10–23)	
<b>6MWT, %pred</b>	49 (41–62)	
<b>MRC sum score, %max</b>	69 (65–83)	
<b>QMT leg score, %pred</b>	36 (26–55)	
<b>FVC upright, %pred</b>	54 (47–68)	
<b>FVC supine, %pred</b>	33 (24–53)	
<b>MIP, %pred</b>	49 (39–64)	
<b>MEP, %pred</b>	50 (39–61)	
<b>Assistive devices, n (% of total) (n = 30)</b>	<b>Start of ERT</b>	<b>End of follow-up</b>
<b>Wheelchair</b>	7 (23)	13 (43)
<b>Partially wheelchair dependent</b>	7 (23)	10 (33)
<b>Fully wheelchair dependent (walking &lt;40 m)</b>	0 (0)	3 (10) <sup>c</sup>
<b>Noninvasive ventilation</b>	7 (23)	24 (80) <sup>cd</sup>

Abbreviations: ERT = enzyme replacement therapy; FVC = forced vital capacity; IQR = interquartile range; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; MRC = Medical Research Council; QMT = quantitative muscle testing; 6MWT = 6-minute walk test; %max = % of maximum outcome; % pred = % of predicted outcome.

<sup>a</sup> Other disease-causing variants on the second allele were c.379\_380del (n = 1), c.-32-13T>G (n = 1), c.118C>T (n = 1), c.1373\_1375del (n = 1), c.1396G>T (n = 1), c.1548G>A (n = 2), c.1636+1G>C (n = 1), c.1717A>C (n = 1), c.172C>T (n = 1), c.1799G>A (n = 2), c.1888+1G>A (n = 1), c.2314T>C (n = 1), c.2608C>T (n = 1), c.461\_469del (n = 1), c.2481+102\_2646+31del (n = 2), and c.573C>A (n = 1).

<sup>b</sup> Antibody titers were determined between 1 and 36 months after the start of ERT. The reported titers indicate the peak titers during this period.<sup>22</sup>

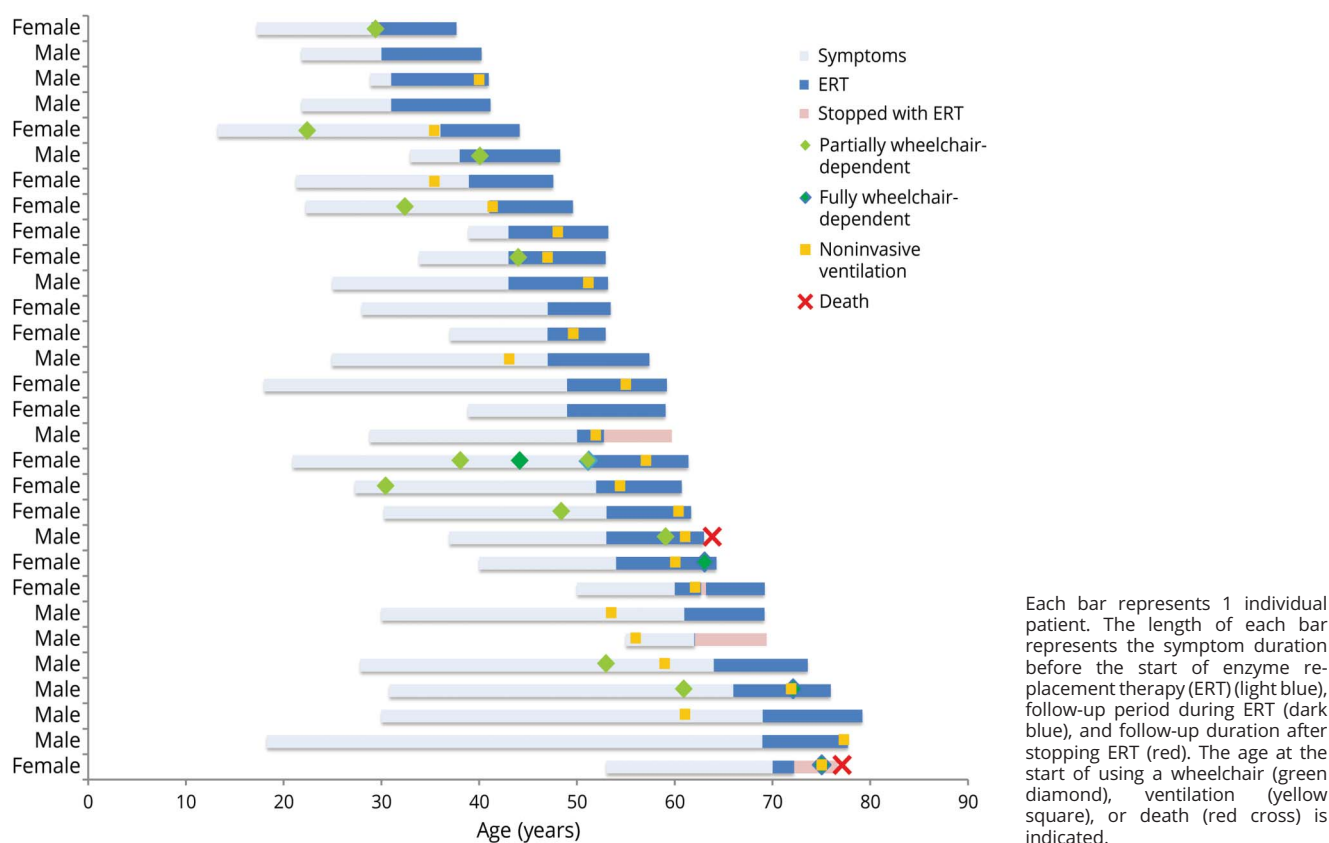
<sup>c</sup> One patient became fully wheelchair dependent and needed noninvasive ventilation after the cessation of ERT.

<sup>d</sup> One patient used noninvasive ventilation because of obstructive sleep apnea syndrome.

During treatment, the walking distance improved during the first 3 years (figure 3A). After this period, we noticed a secondary decline; at the 10-year treatment point, the average 6MWT was lower than at the start of treatment (−22.2 pp,

$p < 0.001$ ). The course over time was independent of sex, disease duration ( $\leq 17$  or  $> 17$  years), and severity at the start of treatment (6MWT at the start of ERT  $\leq 50\%$  or  $> 50\%$ , FVC upright at the start of ERT  $\leq 55\%$  or  $> 55\%$ ).

**Figure 2** Disease course of the individual patients over time (n = 30)



Two patients became fully wheelchair dependent during the treatment period (after 2.8 and 8.7 years of ERT), while another 6 patients were not able to perform the 6MWT anymore because of the high risk of falling. In total, 13 patients (43%) were partially or fully wheelchair dependent at the end of follow-up compared to 7 patients (23%) at the start of ERT.

Relative to the start of treatment, MRC sum score and QMT leg score were also lower after 10 years of ERT (figure 3, B and C). Response to ERT on the MRC sum score was influenced by sex and walking ability at the start of treatment. Men with a baseline walking ability >50% did best (−5.5 pp,  $p = 0.05$ ), while women with a walking ability ≤50% had the greatest decline (−10.5 pp,  $p < 0.001$ ). The decline was −6.8 pp ( $p = 0.001$ ) in men with 6MWT ≤50% and −9.2 pp ( $p < 0.001$ ) in women with baseline 6MWT >50%. QMT leg score decreased by −7.5 pp after 10 years of treatment ( $p = 0.002$ ).

### Pulmonary function

At the start of ERT, median FVC in the upright position was 54% of predicted (IQR 47%–68%) and in the supine position was 33% of predicted (IQR 24%–53%) (table). Overall, FVC in the upright position was relatively stable over the first 5 years of treatment. However, after this period, a decline was observed (figure 4A). After 10 years of treatment, upright FVC had decreased by −11 pp ( $p < 0.001$ ). FVC in supine

position declined slowly in a linear way from the start of treatment (−9.2 pp at the 10-year time-point,  $p < 0.001$ ; figure 4B). MIP and MEP data showed a rather stable course over 10 years of treatment (−1.8 and −2.5 pp at the 10-year time-point,  $p = \text{NS}$ ; figure 4, C and D). Sex, disease duration, and baseline disease severity did not significantly alter the disease course on ERT.

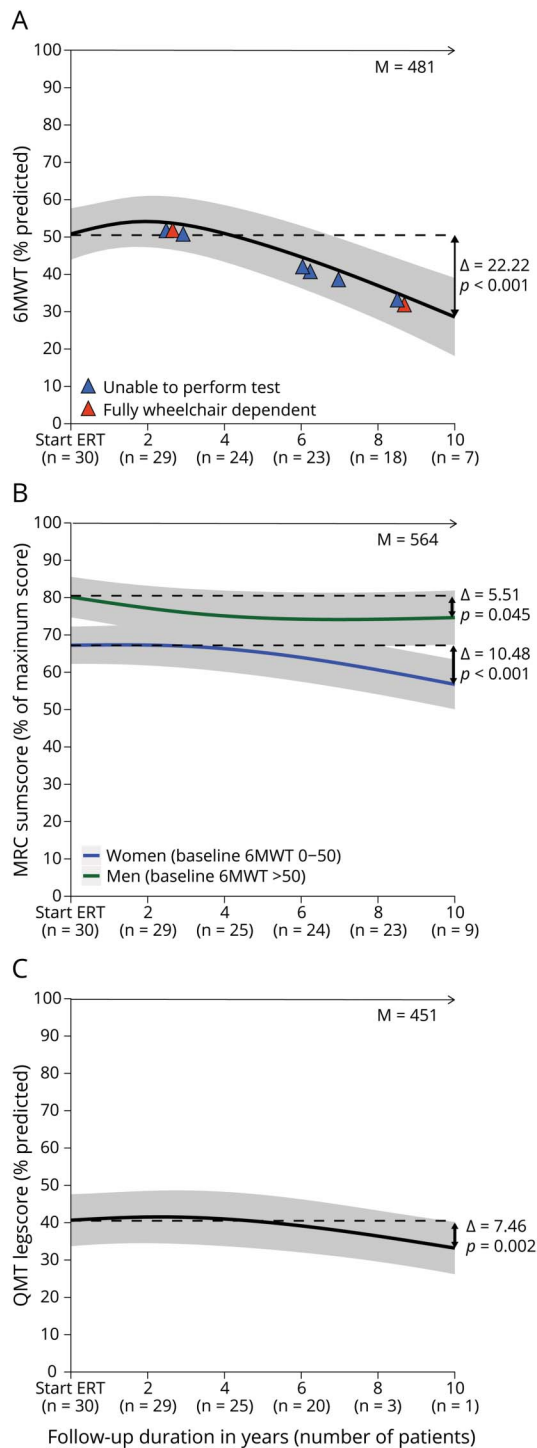
Relative to the extrapolated natural course, patients had better pulmonary function parameters at 10 years of ERT (figure 4, E and F). Their FVC in the upright position was 13.2 pp higher ( $p < 0.001$ ), while their FVC in supine position was 8.5 pp higher ( $p = \text{NS}$ ).

During follow-up, between 4.8 and 9.1 years after the start of ERT, 5 patients were no longer able to perform the measurements in the supine position due to severe orthopnea or full wheelchair dependency. By study end, 24 patients (80%) needed noninvasive ventilation compared to 7 patients (23%) at the start of ERT.

### Individual response to ERT

We analyzed the individual course during ERT for 29 patients. One patient received ERT for 1 month only due to severe infusion-associated reactions and was thus excluded from this specific analysis.

**Figure 3** Effect of ERT on walking ability and muscle strength



Disease course at the group level after the start of enzyme replacement therapy (ERT) for (A) 6-minute walk test (6MWT), (B) Medical Research Council (MRC) sum score, and (C) QMT leg score. Solid lines represent the measured course during treatment. The 95% confidence intervals are shown in gray. For 6MWT, the triangles mark the time point from which individual patients were not able to perform the test due to the risk of falling (blue triangle) or full wheelchair dependency (red triangle). For MRC sum score, the disease courses of the best (men, baseline 6MWT >50% predicted) and worst (women, baseline 6MWT ≤50% predicted) subgroups are shown. The other 2 subgroups (men, baseline 6MWT ≤50% predicted; women, baseline 6MWT >50% predicted) had an intermediate course. M = total number of measurements; n = number of patients at that time of follow-up.

As an initial response, 24 patients (83%) showed stabilization or improvement in their distance walked in 6 minutes compared with the start of ERT, interpreted as a positive response. For the other outcomes, we saw similar patterns: for MRC sum score, 17 patients (59%) had an initial positive response to ERT; for QMT leg score, 22 patients (76%); for FVC upright, 20 patients (69%); and for FVC supine, 19 patients (66%) (figure 5).

A substantial number of patients had a secondary deterioration after an initial positive response to ERT (6MWT, n = 15 of 24 [63%]; MRC sum score, n = 6 of 17 [35%]; QMT leg score, n = 6 of 22 [27%]; FVC upright, n = 11 of 20 [55%]; FVC supine, n = 9 of 19 [47%]). The time point of this change in disease course differed for individual patients; some patients had a change in course after the first 1 to 2 years of treatment, while other patients seemed to respond well up to 7 to 8 years of treatment.

Notably, for FVC in the upright position, 3 patients (10%) showed an initial decline followed by a secondary stabilization. This stabilization coincided with the start of noninvasive mechanical ventilation.

Relative to the start of ERT, at their last follow-up measurement, 34% of patients had better or similar 6MWT distance, 17% had better or similar MRC sum score, and 31% had better or similar FVC in the upright or supine position (figure 5).

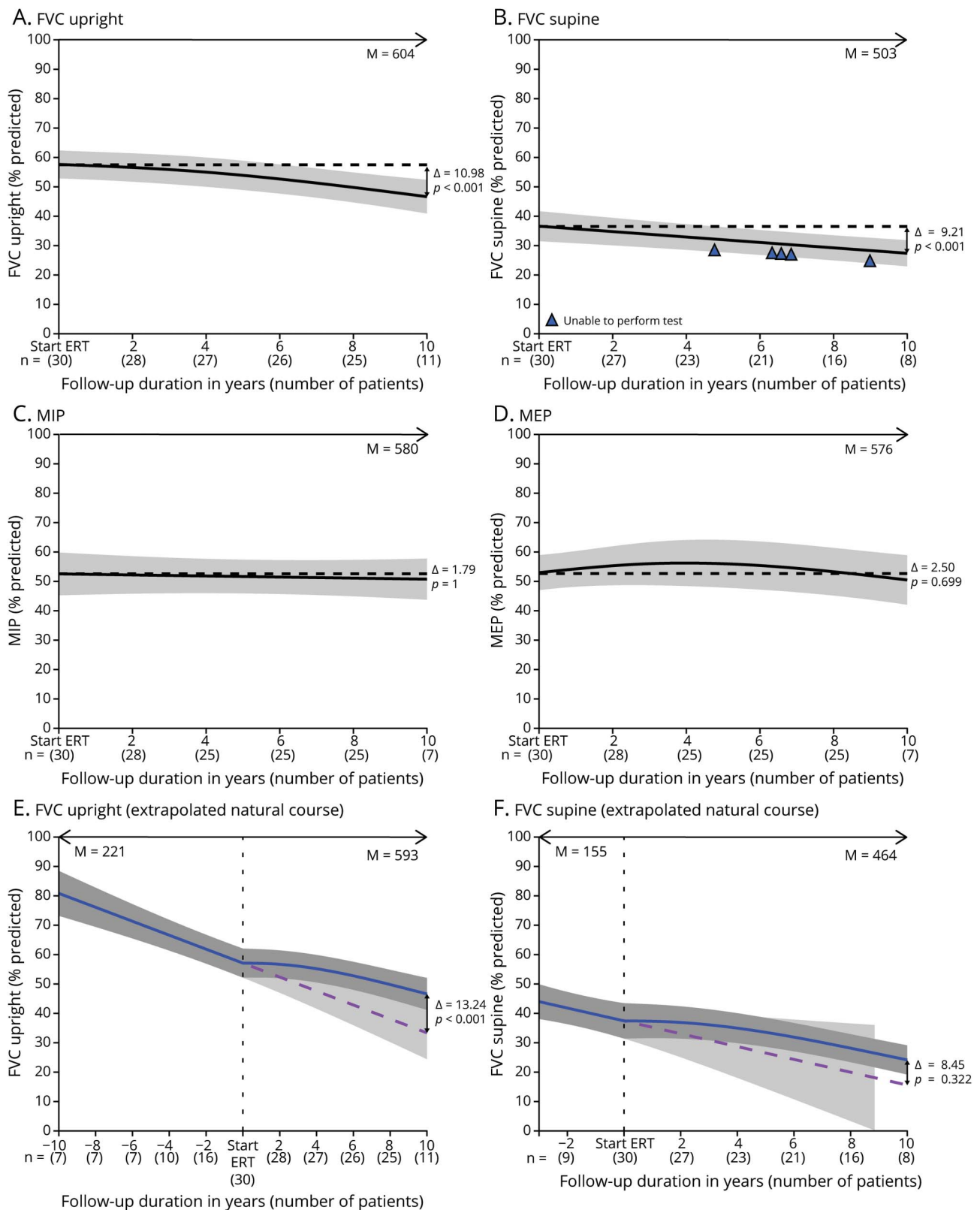
A combined analysis for effect of ERT on 6MWT and upright FVC, which were coprimary endpoints in the LOTS study, showed that 27 patients (93%) had at least a positive response to ERT in 6MWT and/or FVC upright for several years (figure 5B). Five of these patients (17% of all patients) had a very good response to ERT, having similar or better scores in both outcomes during the entire treatment period. Twenty-two patients (76% of all patients) showed a secondary decline in 1 or both outcomes. Only 2 patients (7% of all patients) had an ongoing decline in both parameters from the start of treatment (figure 5C). At their last follow-up measurement, 15 patients (52%) had equal or better 6MWT and/or FVC upright compared to baseline.

There were no obvious differences with respect to their clinical condition at baseline or ancillary investigations (e.g., genotype, antibody peak titers) between the patients with an overall positive response on ERT and those with an ongoing decline.

### Safety

ERT was discontinued in 2 patients (1 and 33 months after the start of treatment) for severe infusion-associated reactions and/or very high antibody titers affecting treatment efficacy.<sup>25</sup> After treatment was stopped, their clinical condition slowly worsened. One other patient stopped

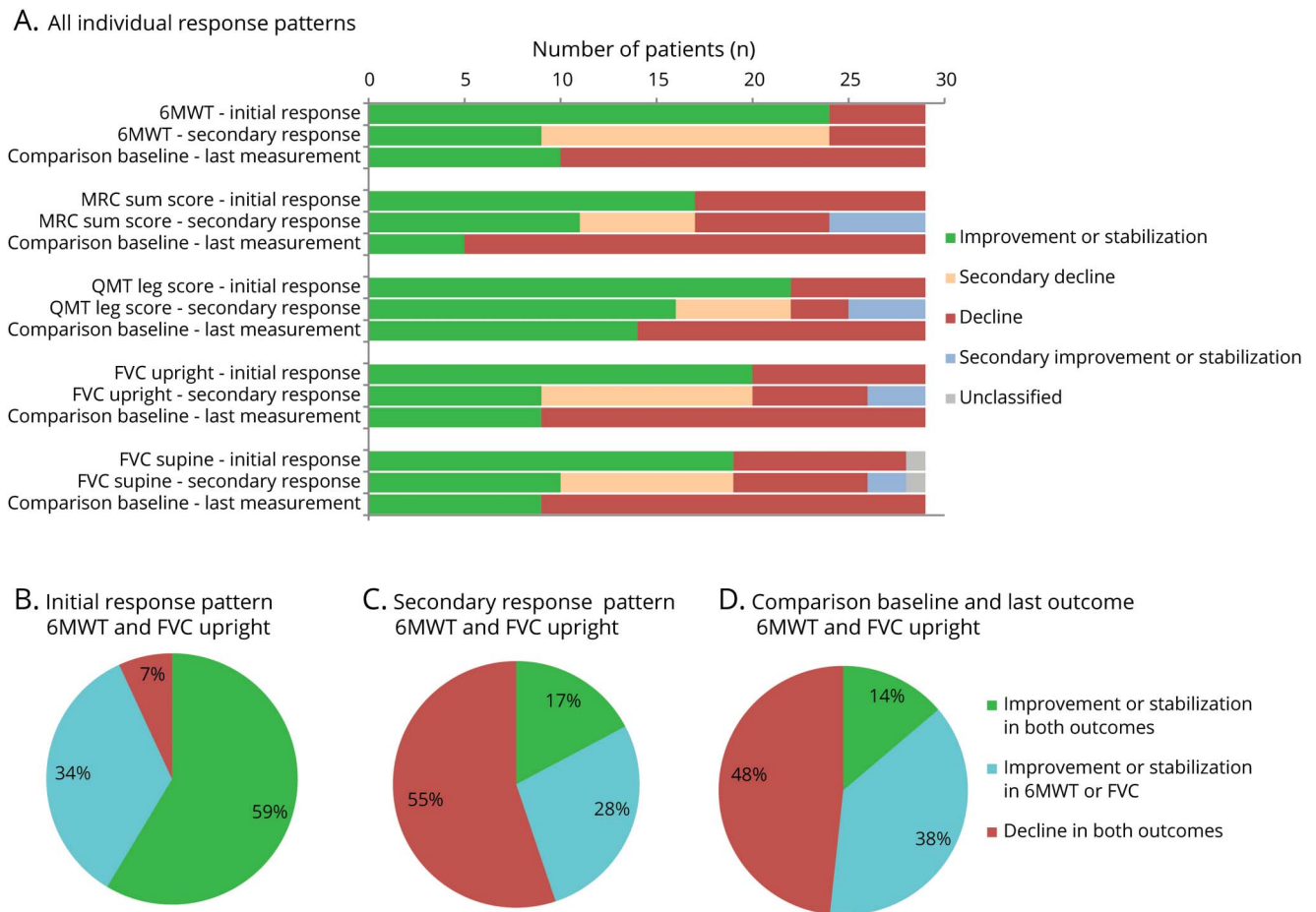
**Figure 4** Effect of ERT on pulmonary function



Disease course at group level after start of enzyme replacement therapy (ERT) for forced vital capacity (FVC) in the upright and supine positions and maximal inspiratory (MIP) and maximal expiratory (MEP) pressures compared to (A–D) baseline or (E and F) the extrapolated natural disease course. Solid lines represent the measured natural course of the disease and/or the course during treatment. Dashed line represents the natural course extrapolated on the basis of natural course data. The 95% confidence intervals are shown in gray. For FVC supine, the triangles mark the time point from which patients were not able to perform the test due to severe orthopnea or full wheelchair dependency. M = total number of measurements; n = number of patients at that time of follow-up.



**Figure 5** Effect of ERT in individual patients



(A) Initial, secondary, and overall disease course at the individual patient level after the start of enzyme replacement therapy (ERT) for 6-minute walk test (6MWT), Medical Research Council (MRC) sum score, quantitative muscle testing (QMT) leg score, and forced vital capacity (FVC) upright and FVC supine separately. Combined individual patients' response on 6MWT and FVC in upright position, subdivided into (B) initial, (C) secondary, and (D) overall response (D). One patient was excluded from this specific analysis due to the short follow-up time on ERT (1 month). The initial and secondary responses of each individual patient were classified by visual judgment of the disease course (using scatterplots). The overall response was calculated by subtracting the last measurement during ERT from that at the start of ERT.

treatment for personal reasons (after 28 months). This patient became wheelchair and ventilator dependent 3 years after cessation of ERT and died 2 years later at the age of 77 years, probably due to respiratory insufficiency. During the study, a second patient, who was already partially wheelchair and ventilation dependent at the start of ERT, died suddenly at 63 years of age after 10 years of treatment with ERT, possibly due to cardiac arrest (no autopsy performed) (figure 2). Neither of the 2 deaths was considered to be directly treatment related. In 1 patient, treatment with ERT was temporarily discontinued on diagnosis of colon and kidney carcinomas. ERT was reintroduced without side effects after cancer treatment.

## Discussion

In this 10-year prospective study on the effects of ERT, we show that 93% of adults with Pompe disease benefit from treatment with ERT during  $\approx 3$  to 5 years. After that period,

many patients experienced a secondary deterioration in walking ability, muscle strength, and/or pulmonary function. For FVC, we could demonstrate that patients' outcomes are better than would have been expected had patients remained untreated, which is to be regarded as a positive effect, taking into account the relentlessly progressive nature of the disease.

Previous studies of up to 5 years of ERT treatment have reported the remarkable change in ERT efficacy during the course of treatment,<sup>8,9,26,27</sup> yet it was unknown how this would evolve with longer-term follow-up. We now see that, at the group level, the initial positive response to treatment is followed by a slow, seemingly linear, decline. However, looking more closely at the individual patients, we found that 5 patients (17%) had a continued positive response on ERT for 10 years, while only 2 patients (7%) were clear non-responders (i.e., they had a decline in walking ability and pulmonary function from the start of treatment). Although

the majority of patients (93%) initially benefited from ERT, it was difficult to predict the timing in change in responsiveness. In some patients, the good response lasted up to 7 to 8 years, while in others, we observed a secondary decline already after 1 to 2 years. What makes it even more complicated is that the response may be discordant among different outcomes, with some patients demonstrating clear improvement in walking ability while deteriorating in pulmonary function ( $n = 2, 7\%$ ) or vice versa ( $n = 2, 7\%$ ). At the end of follow-up, half of the patients had an improved or stable walking ability, pulmonary function, or both. For the individual analyses per patient, insufficient data on the period before start of ERT were available to compare their course on treatment with their natural disease progression. It could well be that a slight decline while on treatment should also be regarded as a positive effect of ERT (e.g., when the rate of decline while not on ERT is greater than the rate of decline on treatment).

We could not identify any obvious explanation for the differences in individual responsiveness. Two patients did not have the common c.-32-13T>G variant but a potentially more severe genotype. Their disease course on ERT was not significantly different. Some studies have suggested that an earlier start of treatment, while patients are still in a better clinical condition, would lead to better efficacy.<sup>9,24</sup> In this study, we did not find evidence for a better treatment effect in patients with a shorter disease duration or less severe disease at the start of treatment compared to those with a longer disease duration or more severe disease. However, our conclusion should be interpreted with some caution because of the limited number of patients across subgroups, plus the fact that they all had some level of disease severity to be included in the initial trial. This relatively severe involvement is probably most clearly reflected by the fact that patients' median supine FVC at start of ERT was only 33% of their predicted normal value, already on the edge of ventilator dependency. This may explain, at least partly, the large increase in the number of patients needing mechanical ventilatory support despite ERT.

As far as we are aware, none of our patients were on a prescribed diet or a specific exercise training program. Because these factors might also influence a patient's response to ERT,<sup>28</sup> this could be a specific topic of further study.

Another explanation for the differences in individuals' responses to treatment could be the presence of antibodies against the recombinant human acid  $\alpha$ -glucosidase. In contrast to patients with classic infantile Pompe disease,<sup>29-31</sup> the relationship between antibodies and clinical outcomes in patients with late-onset disease is not clear. Studies so far, containing data for up to 5 years of ERT treatment, have failed to show a clear correlation between antibody titers and patients' individual response to ERT.<sup>22,23</sup>

In our study, 9 patients (30%) developed high peak antibody titers ( $>1:31,250$ ) during the first 3 years of ERT. Notably, 3 of the 5 patients with a continued positive response to ERT over 10 years on FVC and walking ability had high peak antibody titers. Unfortunately, antibody titers were available only for the first years on treatment; therefore, it cannot be ruled out that they may be of importance in treatment efficacy at a later stage. The role of antibody formation in late-onset Pompe disease should thus be subject of further study.

Factors that can be hypothesized to influence treatment-efficacy are, among others, the content of mannose-6-phosphate (M6P) groups on the recombinant enzyme (which is currently low), variability in the number of M6P/insulin-like growth factor II receptors expressed at the muscle cell surface, the amount of autophagic buildup impeding proper intracellular trafficking and processing of the therapeutic enzyme, and the accessibility of the enzyme to stored glycogen within the muscle cells.<sup>32-35</sup> This is why next-generation therapies are directed at rescuing the disrupted lysosomal glycogen degradation pathway through improved targeting of the M6P/insulin-like growth factor II receptor, responsible for uptake of the infused enzyme and mediating transport to the lysosomes. In addition, we have shown recently that in infants higher dosing (40 mg/kg/wk) resulted in better ventilator-free survival and motor outcome.<sup>36</sup> For obvious reasons (i.e., the very costly treatment), higher dosing strategies have never been applied in adult patients, but insufficient dosing might explain part of the deterioration we observe.

When evaluating therapeutic interventions, one should always search for outcome measures that best capture clinical meaningful changes. In this context, it was notable to see that, during the 10-year follow-up, 8 patients were not able to perform the 6MWT anymore either because they had become fully wheelchair dependent or because the evaluator thought the risk of falling was too high. In addition, 5 patients were no longer able to endure the supine position for FVC testing. For these very severely affected patients, but also for patients with still minimal weakness, additional measurements should be considered to evaluate their long-term treatment response. For patients who are still able to walk short distances, gait analysis may be of additional value. Here, velocity, duration of stance phase, and step and stride length can be evaluated, as well as when walking devices are used.<sup>37-39</sup> For a more detailed evaluation of pulmonary function, spirometry-controlled MRI or ultrasonography of the diaphragm may be appropriate.<sup>40-42</sup> In addition, evaluation of muscle function could possibly be more reliably evaluated with patient-reported outcome measures, reporting activities in daily life.<sup>43,44</sup>

In 2017, European consensus guidelines were published on the use of ERT in adult patients with Pompe disease.<sup>45</sup> Within this consensus statement, recommendations on when to stop

ERT treatment are posed. One of these recommendations is to reconsider whether ERT should be continued if skeletal muscle function or respiratory function has not stabilized or improved in the first 2 years after the start of treatment. Our study showed that 93% of all patients had initial benefit of ERT. Two patients (7%) deteriorated from the beginning, despite ERT; in these patients, we are considering the cessation of ERT.

Our study shows that there is large interindividual variation not only in response patterns but also in duration of treatment efficacy and that the treatment effects may be discordant across multiple outcomes. Because we do not yet fully understand the factors underlying the great variability in treatment response, predicting before treatment initiation who will do well or not is currently not possible. Although >90% of patients benefit from ERT for the first 3 to 5 years, the observed secondary decline, suggesting diminished therapeutic efficacy over time, raises concerns and stresses the need for next-generation therapies.

## Disclosure

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## Appendix (continued)

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