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# Fabry disease under enzyme replacement therapy—new insights in efficacy of different dosages

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## ABSTRACT

**Background.** Fabry patients on reduced dose of agalsidase-beta or after switch to agalsidase-alfa show a decline in estimated glomerular filtration rate (eGFR) and an increase of the Mainz Severity Score Index.

**Methods.** In this prospective observational study, we assessed end-organ damage and clinical symptoms in 112 patients who had received agalsidase-beta (1.0 mg/kg) for >1 year, who were (i) non-randomly assigned to continue this treatment regime (regular-dose group, $n = 37$); (ii) received a reduced dose of agalsidase-beta and subsequent switch to agalsidase-alfa (0.2 mg/kg) or a direct switch to 0.2 mg/kg agalsidase-alfa (switch group, $n = 38$); or (iii) were re-switched to agalsidase-beta after receiving agalsidase-alfa for at least 12 months (re-switch group, $n = 37$) with a median follow-up of 53 (38–57) months.

**Results.** eGFR of patients in the regular-dose group remained stable. Patients in the switch group showed an annual eGFR loss of $-4.6 \pm 9.1$ mL/min/1.73 m$^2$ ($P < 0.05$). Patients in the

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re-switch group also had an eGFR loss of − 2.2 ± 4.4 mL/min/1.73 m$^2$ after re-switch to agalsidase-beta, but to a lower degree compared with the switch group ($P < 0.05$). Patients in the re-switch group suffered less frequently from diarrhoea (relative risk 0.42; 95% confidence interval 0.19–0.93; $P = 0.02$). Lyso-Gb3 remained stable in the switch ($P = 0.97$) and the regular-dose ($P = 0.48$) groups, but decreased in the re-switch group after change of the therapy regimen ($P < 0.05$).

**Conclusions.** After switch to agalsidase-alfa, Fabry patients experienced a continuous decline in eGFR, while this decline was attenuated in patients who were re-switched to agalsidase-beta. Decreasing lyso-Gb3 levels may indicate a better treatment response in the latter group.

**Keywords:** agalsidase, eGFR, Fabry disease, lyso-Gb3, switch

## INTRODUCTION

Fabry disease (FD) is an X-linked rare progressive multisystemic disorder resulting from lysosomal enzyme alpha-galactosidase A (GLA) deficiency, which is treatable with recombinant enzyme replacement therapy (ERT) since 2001 and chaperone therapy (Migalastat, Amicus) since May 2016. ERT is available as agalsidase-alfa (Replagal, Shire) and agalsidase-beta (Fabrazyme, Sanofi Genzyme) [1, 2]. The worldwide shortage of agalsidase-beta supply (from June 2009 to January 2012) resulted in a change of treatment regimen in those patients who had formerly received agalsidase-beta in a standard dose [1.0 mg/kg body weight (BW) every other week (e.o.w.)]. In these patients, the dosage was either reduced (0.3–0.5 mg/kg BW e.o.w.) or treatment was switched to agalsidase-alfa (0.2 mg/kg BW e.o.w.) [3–8]. ERT has been shown to stabilize or at least slow down disease progression by preventing systemic cellular accumulation of mainly globotriaosylceramide (Gb3) [9–15]. However, our recent observations of patients on dose-reduction of agalsidase-beta suggested a decline in estimated glomerular filtration rate (eGFR) and an increase of Fabry-related clinical symptoms [7, 8]. In addition, switching to agalsidase-alfa also resulted in an increase of Fabry-related symptoms and a decline of estimated glomerular filtration rate (eGFR), even if it did not lead to adverse clinical events. With respect to eGFR, our findings were supported by Tøndel *et al.* and later by Skrunes *et al.*, who demonstrated a dose-dependent Gb3 clearance in podocytes [15–17]. However, the long-term effect of a dose reduction and/or the re-switch to a standard dose of agalsidase-beta on patients' outcome and disease progression still remains elusive.

In the current study, we assessed clinical stability and safety after switch to agalsidase-alfa and outcomes after re-switch to agalsidase-beta standard dose after 53 (range 38–57) months of observation with special focus on clinical events, renal end-organ damage, disease-related clinical symptoms as well as disease severity as prolongation of previous results [7, 8].

## MATERIALS AND METHODS

### Study design

In total, 112 patients (43 females) with genetically confirmed FD from three German Fabry centres (Berlin, Münster and Würzburg) were initially recruited and followed in a prospective observational study. Inclusion criteria were (i) ≥18 years of age and genetically confirmed FD, (ii) ≥12 months of ERT with full dose of agalsidase-beta (1.0 mg/kg e.o.w.) before inclusion and (iii) written informed consent for examinations and participation in the study as well as for molecular analysis and publication. All investigations were performed after approval of the ethics committees of the participating centres (project number: 2011–347-f).

The current observational study was initiated during the period of restriction of agalsidase-beta supply. Three complete data sets of each patient were included for further analysis (baseline, first and second long-term follow-up). As additional patients participated in the current study, the absolute number of patients differs. As previously described, ≥12 months stable on one of the available therapies was regarded as sufficient to be allocated to the specific treatment group. Finally, of the 112 patients included in this study, 99 and 89 fulfilled inclusion criteria in the 1-year follow-up [7] and in the 2-year follow-up study [8], respectively.

At baseline (baseline visit; Figure 1), all patients ($n = 112$) had been stable on therapy with agalsidase-beta (1.0 mg/kg e.o.w.) for ≥12 months. In all, 37 patients continued this treatment for the entire observation period (regular-dose group, $n = 37$; Figure 1). Due to the restricted supply of agalsidase-beta, 75 patients (67%) were switched to agalsidase-alfa (0.2 mg/kg e.o.w.; $n = 49$) or first received agalsidase-beta in reduced dose (0.5 mg/kg e.o.w.) and then subsequently switched to agalsidase-alfa (0.2 mg/kg e.o.w.; $n = 26$). After the end of agalsidase-beta shortage, some patients were subsequently re-switched to full dose of agalsidase-beta (1.0 mg/kg e.o.w; re-switch group, $n = 37$; Figure 1), while some patients remained on agalsidase-alfa (switch group, $n = 38$; Figure 1). After being stable on individual therapy for ≥12 months, the first follow-up examination was performed (first long-term follow-up visit). The second follow-up examination (second long-term follow-up visit) was performed after being stable on therapy for another period of ≥12 months (Figure 1).

Routine clinical assessment (including cardiac, renal and neurological parameters) was performed as previously reported

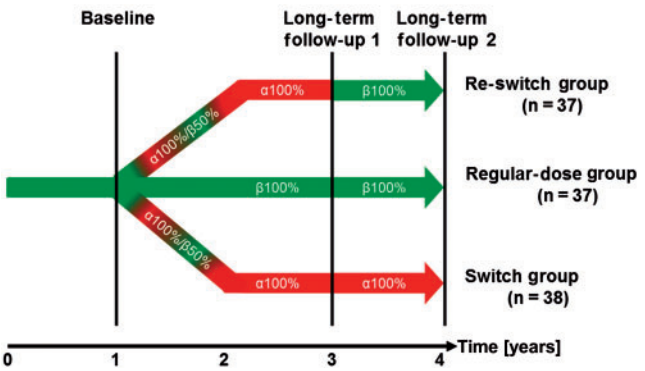


FIGURE 1: Overview of the general study design. Allocation of the three treatment groups (regular-dose, switch, re-switch) according to the therapy regimen for the last 12 months. Red arrows: patients treated with agalsidase-alfa, green arrows: patients treated with agalsidase-beta.

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[7, 8]. Clinical examination and standard echocardiographic measurements were performed annually in all patients at the participating centres. The eGFR was quantified by using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI)-based equation on the basis of serum creatinine ($eGFR_{creat}$) [18], cystatin C levels ($eGFR_{cys}$) [19] and a combination of creatinine and cystatin C ($eGFR_{creat-cys}$) [19] and albuminuria (ACR) from spot urine. Microalbuminuria was defined as an ACR between 30 and 300 mg albumin per gram of creatinine. For the eGFR analyses, patients under dialysis were excluded. Neurological symptoms were assessed using a standardized clinical interview focusing on pain and history of stroke/transient ischaemic attack (TIA) as well as neurography of the sural nerve. All investigations were performed according to the Declaration of Helsinki.

Based on the observational design, patients were not randomized. The long-term treatment strategy was decided by the physicians at each study centre. As previously described, this resulted in inhomogeneous treatment groups with more severely affected patients in the regular-dose agalsidase-beta group, while the switch and re-switch groups did not differ significantly in clinical settings. The regular-dose group included more male patients, presenting with lower GLA activity compared with the switch and re-switch groups (both $P < 0.05$).

The regular-dose group included 22 (60%) patients with nonsense mutations, the switch group 20 (55%) and the re-switch group 13 patients (35%; $P = 0.10$) (Supplementary data, Table S1). We identified 55 different GLA mutations in our patients. In all, six patients presented with a 'mild' or 'late-onset' phenotype. In detail, two of these patients carried the p.A143T mutation (1× regular-dose group; 1× switch group); three patients the p.N215S mutation (1× regular-dose group, 2× re-switch group) and one patient carried the IVS0-10 C > T variant with an FD-typical neurological phenotype (re-switch group). For genotype analyses, missense mutations were defined as single nucleotide exchanges, resulting in single amino acid substitutions. Nonsense mutations included single nucleotide exchanges, resulting in a stop codon (termination), deletion or insertions of nucleotides resulting in a frame shift or large deletions within the protein, or splice site mutations, resulting in altered splice products of mRNA. Serum samples for neutralizing anti-drug antibodies determination were available for at least 52 male patients. In all, 38.5% of tested males were inhibition-positive according to definitions from recent literature [20, 21]. A total of 10 patients (59%) within the regular dose-group, 6 patients (32%) within the re-switch group and 4 patients (25%) within the switch group presented with inhibitory antibodies ($P = 0.10$).

### Outcome

Outcome was assessed at each clinical visit for (i) Fabry-related clinical events, (ii) change in organ function and (iii) Fabry-related symptoms. Clinical events were defined as follows: (i) cardiac arrhythmia requiring an implantable cardioverter defibrillator, myocardial infarction, coronary artery bypass grafting and percutaneous transluminal coronary angioplasty, (ii) progression of renal disease to CKD stage 5 [eGFR $\leq$15 mL/min/1.73 $m^2$ (with at least 30% decrease of eGFR), kidney transplantation or dialysis] and (iii) new stroke/transitory ischaemic attack (TIA).

Serious clinical events were defined as death resulting from above-defined clinical events.

Changes in organ function and/or structure were registered for the heart (septal and posterior wall thickness, ejection fraction) and for the kidney (annual eGFR slopes, ACR). Changes in FD-related symptoms were classified according to appearance of gastrointestinal pain, diarrhoea, hypo- or anhidrosis, tinnitus and Fabry-associated pain (i.e. pain attacks, permanent pain or pain crises) [22]. In addition, the Mainz Severity Score Index (MSSI) [23] was assessed as a score for disease burden.

For plasma lyso-Gb3 determination, lysoCeramide was used as reference (Matreya LLC, Pleasant Gap, PA, USA) and D5-Fluticasone Propionate (EJY Tech, Inc., Rockville, MD, USA) served as internal standard. Plasma lyso-Gb3 levels were measured in one laboratory (University of Rostock, Germany). ERT inhibition assays to assess the presence of neutralizing anti-drug antibodies were performed as reported elsewhere [20]. Patients with a mean ERT inhibition >50% were designated as ERT inhibition positive according to recent literature [20, 21, 24].

### Data analyses

Data are presented as the mean ± standard deviation (SD), median (quartiles) or number (percentage), where appropriate. Baseline and follow-up values were compared using paired tests (Student's or Wilcoxon), where appropriate. Differences between groups were tested via one-way analysis of variance (ANOVA) for continuous variables or Fisher's exact test for categorical variables. For categorical data, the chi-square or Fisher's exact tests were used. All differences were tested two-sided. P-values <0.05 were considered statistically significant. Data were analysed using SPSS software, version 18.0 (SPSS, Inc., Chicago, IL, USA).

## RESULTS

In total, 112 patients were observed over a period of 53 (range 38–57) months. A diagnostic workup was performed as previously reported [7]. Figure 1 illustrates timelines and agalsidase doses in the three treatment groups (regular-dose group, $n = 37$; switch group, $n = 38$; re-switch group, $n = 37$). Baseline characteristics are presented in Table 1. Mean age of Fabry patients was 45 ± 13 years, 43 (38%) were female patients. All patients received agalsidase-beta (1.0 mg/kg e.o.w.) for ≥12 months, mean duration of ERT at baseline was 31 (12–60) months.

Fabry-associated symptoms (i.e. angiokeratoma, diarrhoea, hypohidrosis and Fabry-related pain attacks) were more frequent in the regular-dose group compared with the switch group ($P < 0.05$). Oedema was more common in the regular-dose and the switch group compared with the re-switch group (both $P < 0.05$). General MSSI was higher in the regular-dose group compared with the re-switch group ($P < 0.05$; Table 1). In addition, patients in the re-switch group received ERT in total for longer than patients in the switch group ($P = 0.05$).

The three groups did not differ at baseline visit in any additional medication [diuretics, renin-angiotensin-aldosterone

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**Table 1. Baseline characteristics**

| Patients | Regular-dose group ($n = 37$) | Switch group ($n = 38$) | Re-switch group ($n = 37$) | Total ($n = 112$) |
|---|---|---|---|---|
| Females, *n* (%) | 8 (22)[a,b] | 19 (50) | 16 (43) | 43 (38) |
| Age, years | 42 ± 13 | 43 ± 13 | 48 ± 12 | 45 ± 13 |
| Weight, kg | 74 ± 20[b] | 70 ± 12[c] | 78 ± 14 | 74 ± 16 |
| Height, cm | 176 ± 8[a] | 171 ± 10 | 173 ± 10 | 173 ± 10 |
| Heart rate, bpm | 63 ± 11 | 67 ± 11 | 64 ± 8 | 65 ± 11 |
| Systolic BP, mmHg | 122 ± 15 | 123 ± 16 | 123 ± 14 | 122 ± 15 |
| Diastolic BP, mmHg | 77 ± 10 | 79 ± 10 | 77 ± 8 | 78 ± 9 |
| Duration of ERT, months | 29 ± 28 | 21 ± 25[c] | 34 ± 6 | 31 ± 29 |
| GLA activity, nmol/min | 0.02 ± 0.02[a,b] | 0.09 ± 0.10 | 0.08 ± 0.12 | 0.06 ± 0.08 |
| Medication | | | | |
| Diuretics, *n* (%) | 11 (30) | 18 (47) | 18 (48) | 47 (42) |
| RAAS blockers, *n* (%) | 21 (57) | 26 (68) | 25 (68) | 72 (64) |
| Analgesics, *n* (%) | 17 (46) | 18 (47) | 23 (62) | 58 (52) |
| Use of premedication, *n* (%) | 2 (5.4) | 2 (5.3) | 1 (2.7) | 5 (4.5) |
| Neutralizing antibodies (male patients) | | | | |
| Serum sample available, *n* (%) | 17 (58.6) | 19 (100) | 16 (76.2) | 52 (75) |
| Antibody positive, *n* (%) | 10 (58.8) | 6 (31.6) | 4 (25) | 20 (38.5) |
| Fabry-typical symptoms | | | | |
| Angiokeratoma, *n* (%) | 23 (62)[a] | 15 (39) | 20 (54) | 58 (52) |
| Hypohidrosis, *n* (%) | 27 (73)[a] | 18 (47) | 19 (51) | 64 (57) |
| Cornea verticillata, *n* (%) | 17 (46) | 14 (37) | 22 (59) | 53 (47) |
| Oedema, *n* (%) | 14 (38)[b] | 9 (24)[c] | 3 (8.1) | 26 (23) |
| Abdominal pain, *n* (%) | 9 (24) | 3 (7.9) | 6 (16) | 18 (16) |
| Diarrhoea, *n* (%) | 12 (32)[a] | 6 (16) | 8 (21) | 26 (23) |
| Tinnitus, *n* (%) | 9 (24) | 8 (21) | 10 (27) | 27 (24) |
| Hypakusis, *n* (%) | 13 (35) | 8 (21) | 8 (22) | 29 (26) |
| Paresthesia, *n* (%) | 21 (57) | 22 (58) | 24 (65) | 67 (60) |
| Chronic pain, *n* (%) | 17 (46) | 17 (45) | 19 (51) | 53 (47) |
| Pain attacks, *n* (%) | 12 (32)[a,b] | 4 (11) | 4 (11) | 20 (18) |
| Pain crisis, *n* (%) | 4 (11) | 6 (16) | 6 (16) | 16 (14) |
| Fatigue, *n* (%) | 10 (27) | 10 (26) | 7 (19) | 27 (24) |
| TIA/stroke, *n* (%) | 8 (22) | 5 (13) | 2 (5.4) | 15 (13) |
| MSSI (general), score | 22 ± 12[b] | 20 ± 11 | 16 ± 9 | 19 ± 12 |

Values are given as mean ± SD or median (quartiles) or number (%), as appropriate. Differences between groups have been tested via one-way ANOVA for continuous variables or Fisher's exact test for categorical variables. BP, blood pressure; RAAS, renin-angiotensin-aldosterone-system.
[a]$P < 0.05$ for regular-dose versus switch group.
[b]$P < 0.05$ for regular-dose versus re-switch group.
[c]$P < 0.05$ for switch versus re-switch group.

system blockers and analgesics (i.e. ibuprofen, tramadol or pregabalin)] (Table 1). During the first and second long-term follow-up, the number of patients receiving medication and drug doses was unchanged (data not shown). For all types of medication, no changes or differences between groups and visits were observed. Patients under agalsidase-alfa tolerated re-switch to agalsidase-beta well. In general, three (8%) patients of the re-switch group developed mild infusion reactions, such as mild fever and increased fatigue after infusions. These patients received premedication with steroids and histamine antagonists directly before infusions.

There were no differences according to renal (Table 2), cardiac and neurological measurements (Table 3) at baseline.

## Outcome for organ function

Due to previous findings [7, 8], we focused our analyses on renal function (i.e. eGFR and ACR). To consider different follow-up periods and baseline values within the groups, eGFR slope was adjusted for duration of follow-up and is presented as annual loss of GFR (mL/min/1.73 $m^2$/year). eGFR was calculated by three different CKD-EPI formulae on the basis of creatinine and cystatine C as stated above. Since the equation that combines creatinine and cystatin C ($eGFR_{creat-cys}$) has been reported as the most precise estimate of GFR [19], eGFR outcomes described within the following are given as $eGFR_{creat-cys}$. eGFR values (independent of the eGFR formula used) remained stable in the regular-dose group until the first long-term follow-up after 21 ± 4 months (Table 4). However, patients in the switch group presented with an annual $eGFR_{creat-cys}$ loss of 6.0 ± 5.1 mL/min/1.73 $m^2$ (baseline versus first long-term follow-up $P = 0.012$), which was comparable to the decline of 5.8 ± 8.9 mL/min/1.73 $m^2$ in the re-switch group (baseline versus first long-term follow-up $P < 0.001$; Table 4). Between the first and second long-term follow-up, $eGFR_{creat-cys}$ values in the regular-dose group were stable ($P = 0.41$). In contrast, patients in the switch group, consistently on therapy with agalsidase-alfa for another 17 ± 3 months, suffered from an additional annual $GFR_{creat-cys}$ decline of 4.6 ± 9.1 mL/min/1.73 $m^2$ ($P < 0.05$). Patients in the re-switch group, who were ≥12 months stable on agalsidase-beta full dose, also showed an additional annual $eGFR_{creat-cys}$ loss of 2.2 ± 4.4 mL/min/1.73 $m^2$ ($P < 0.05$), but the decline was attenuated compared with the switch group ($P < 0.05$) and showed no difference with respect to the regular-dose group ($P = 0.72$, Figure 2, Table 4).

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**Table 2. Baseline renal measures**

| Measurements | Regular-dose group ($n = 37$) | Switch group ($n = 38$) | Re-switch group ($n = 37$) | Total ($n = 112$) |
|---|---|---|---|---|
| Creatinine, mg/dL | 2.0 ± 2.4[a,b] | 1.6 ± 2.2 | 1.3 ± 1.1 | 1.6 ± 2.0 |
| *Creatinine, mg/dL | 1.1 ± 0.4 | 1.0 ± 0.4 | 1.2 ± 0.7 | 1.1 ± 0.5 |
| Cystatin C, mg/L | 1.5 ± 1.3[a,b] | 1.1 ± 0.9 | 1.1 ± 0.8 | 1.2 ± 0.9 |
| *Cystatin C, mg/L | 0.9 ± 0.3 | 0.9 ± 0.4 | 1.0 ± 0.5 | 1.0 ± 0.4 |
| eGFR, mL/min/1.73 $m^2$ | | | | |
| $eGFR_{creat-cys}$ | 71 ± 40[a] | 89 ± 34 | 80 ± 34 | 80 ± 39 |
| *$eGFR_{creat-cys}$ | 87 ± 38 | 95 ± 34 | 87 ± 38 | 90 ± 36 |
| $eGFR_{creat}$ | 80 ± 51[a] | 93 ± 49 | 89 ± 44 | 87 ± 48 |
| *$eGFR_{creat}$ | 84 ± 28 | 87 ± 34 | 79 ± 29 | 83 ± 29 |
| ACR, mg/g creatinine | 99 (4–678) | 92 (15–466) | 96 (13–860) | 96 (14–651) |
| Albuminuria, *n* (%) | 14 (38) | 16 (42) | 13 (35) | 43 (38) |
| Hemoglobin, mg/dL | 13.7 ± 1.5 | 13.3 ± 1.2 | 13.8 ± 1.1 | 13.6 ± 1.3 |
| Kidney transplantation, *n* (%) | 3 (8.1) | 4 (10) | 2 (5.4) | 9 (8.1) |
| Dialysis, *n* (%) | 9 (24)[b] | 6 (16) | 3 (8.1) | 18 (16) |
| Hyperfiltration, *n* (%) | 4 (11) | 5 (13) | 3 (8.1) | 12 (11) |

Values are given as mean ± SD, median (quartiles) or *n* (%) as appropriate. Variables indicated with an asterisk omit patients with kidney transplantation, dialysis or hyperfiltration. Statistical significance was tested using paired *t*-test or Kruskal–Wallis test, as appropriate; no significant findings are reported. Differences between groups have been tested via one-way ANOVA for continuous variables or Fisher's exact test for categorical variables. $eGFR_{creat}$ and $eGFR_{creat-cys}$ are calculated via the CKD-EPI formulae. Albuminuria, ACR >30 mg/g albumin/creatinine; hyperfiltration, $eGFR_{creat}$ >120 mL/min per 1.73 $m^2$. ACR, albumin-creatinine ratio.
[a]$P < 0.05$ for regular-dose versus switch group.
[b]$P < 0.05$ for regular-dose versus re-switch group.

**Table 3. Baseline cardiac and neurologic measures**

| Measurements | **Regular-dose group** ($n = 37$) | **Switch group** ($n = 38$) | **Re-switch group** ($n = 37$) | **Total** ($n = 112$) |
|---|---|---|---|---|
| Cardiac measures | | | | |
| NYHA class | | | | |
| I | 4 (11%) | 2 (5.3%) | 8 (22%) | 14 (13%) |
| II | 21 (57%) | 23 (61%) | 16 (43%) | 60 (54%) |
| III | 10 (27%) | 10 (26%) | 10 (27%) | 30 (27%) |
| IV | 2 (5.4%) | 3 (7.9%) | 3 (8.1%) | 8 (7.1%) |
| LVDd, mm | 48.0 ± 6.4 | 45.4 ± 6.3 | 47.9 ± 5.9 | 47 ± 6.3 |
| LVSd, mm | 31.6 ± 7.1 | 29.8 ± 6.9 | 30.3 ± 6.4 | 31 ± 6.8 |
| LVSd, mm | 12.7 ± 3.0 | 13.2 ± 3.2 | 13.1 ± 3.2 | 12.9 ± 3.1 |
| LVPWd, mm | 12.3 ± 2.3 | 12.0 ± 2.9 | 12.6 ± 2.2 | 12.3 ± 2.5 |
| LVEF, % | 63 ± 8 | 65.1 ± 7.2 | 62 ± 5 | 63 ± 7.1 |
| ECG abnormalities | 9 (24%) | 12 (32%) | 7 (19%) | 28 (25%) |
| Pacemaker | 3 (8.1%) | 1 (2.6%) | 2 (5.4%) | 6 (5.4%) |
| Neurologic measures | | | | |
| CES-D score | 16 (5–24) | 16 (7–23) | 9 (5–20) | 13 (6–23) |
| GCPS 2 (maximum pain) | 5 (1–6) | 7 (0–8) | 4 (2–8) | 5 (1–8) |
| GCPS 5 (impairment) | 0 (0–3) | 2 (0–7) | 1 (0–3) | 1 (0–3) |
| NPSI | 0 (0–0.1) | 0 (0–0.2) | 0.1 (0–0.3) | 0 (0–0.1) |
| SNAP, µV | 14 (6–20) | 17 (9–21) | 17 (6–18) | 16 (7–19) |
| NCV, m/s | 44 (39–47) | 47 (42–51) | 43 (39–46) | 44 (40–49) |

Values are given as mean ± SD, median (quartiles) or *n* (%), as appropriate. Differences between groups were tested via analysis of covariance (ANCOVA) with *post hoc* testing, Kruskal–Wallis and subsequent Mann–Whitney U-test, or chi-square, as appropriate (for details, see Materials and methods). CES-D, Center for Epidemiologic Studies-Depression scale; ECG, electrocardiogram; GCPS, Graded Chronic Pain Scale; LVDd, left ventricular diameter in diastole; LVEF, left ventricular ejection fraction; LVPWd, left ventricular posterior wall diameter in diastole; LVSd, left ventricular septum thickness in diastole; LVSd, left ventricular diameter in systole; NCV, nerve conduction velocity; NPSI, Neuropathic Pain Symptom Inventory; NYHA, New York Heart Association; SNAP, sensory nerve action potential.

Comparable to previous results [8], values for ACR did not significantly differ between baseline, long-term follow-up 1 or 2 (Supplementary data, Table S2). No changes were observed during the follow-up period for cardiac parameters (Table 5).

### Outcome for clinical symptoms

Patients under full-dose therapy with agalsidase-beta showed no changes during the entire observational period (Table 6). Between baseline and the second long-term follow-up, frequency of abdominal pain increased in patients within the switch group [relative risk (RR) 1.95; 95% confidence interval (CI) 1.33–2.85; $P < 0.05$] and the re-switch group (RR 1.64; 95% CI 1.08–2.51; $P < 0.05$; Table 6). Patients in the switch group more often reported diarrhoea in the first long-term follow-up period ($P < 0.05$; Table 6). Between the first and the second long-term follow-up, the frequency of abdominal pain remained stable in both groups on agalsidase-beta but significantly increased in the switch group ($P < 0.05$). Frequency of diarrhoea remained stable in the regular-dose and the switch group, but decreased significantly in the re-switch group

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**Table 4. Outcomes for glomerular filtration rates**

| Measurements | Baseline | LTFU 1 | Baseline to LTFU 1 | | LTFU 2 | LTFU 1 to LTFU 2 | |
|---|---|---|---|---|---|---|---|
| | | | Change mL/min/1.73 $m^2$/year | Per cent change eGFR per year | | Change in mL/min/1.73 $m^2$/year | Per cent change in eGFR per year |
| Regular-dose group ($n = 37$) | | | | | | | |
| $eGFR_{creat-cys}$ | 89 ± 36 | 93 ± 38 | 4.2 ± 15.8[c,d] | 4.7 ± 19.1[c,d] | 90 ± 38 | −2.4 ± 13.2[c] | −2.6 ± 14.9[c] |
| $eGFR_{creat}$ | 88 ± 30 | 92 ± 32 | 5.0 ± 14.2[c,d] | 5.6 ± 16.3 [c,d] | 89 ± 37 | −3.2 ± 11.2[c] | −3.7 ± 13.1[c] |
| $eGFR_{cys}$ | 99 ± 35 | 104 ± 34 | 6.1 ± 19.2 | 6.6 ± 19.2 | 99 ± 45 | −2.2 ± 9.8 | −2.3 ± 10.1 |
| Switch group ($n = 38$) | | | | | | | |
| $eGFR_{creat-cys}$ | 93 ± 37[a] | 81 ± 28[b] | −6.0 ± 5.1 | −5.5 ± 6.8 | 75 ± 31 | −4.6 ± 9.1[e] | −5.7 ± 14.3[e] |
| $eGFR_{creat}$ | 98 ± 34[a] | 83 ± 31[b] | −7.2 ± 9.3 | −6.2 ± 11.3 | 72 ± 32 | −8.1 ± 12.1[e] | −10.6 ± 16.0[e] |
| $eGFR_{cys}$ | 107 ± 39 | 93 ± 29 | −8.9 ± 9.9 | −8.8 ± 11.1 | 89 ± 39 | −5.4 ± 14.3 | −6.0 ± 16.3 |
| Re-switch group ($n = 37$) | | | | | | | |
| $eGFR_{creat-cys}$ | 84 ± 31[a] | 76 ± 25[b] | −5.8 ± 8.9 | −6.6 ± 12.5 | 74 ± 31 | −2.2 ± 4.4 | −3.2 ± 5.9 |
| $eGFR_{creat}$ | 92 ± 25[a] | 78 ± 23[b] | −5.6 ± 7.7 | −7.5 ± 10.8 | 77 ± 24 | −1.8 ± 5.2 | −5.3 ± 6.9 |
| $eGFR_{cys}$ | 97 ± 29 | 87 ± 36 | −6.1 ± 8.9 | −5.8 ± 9.9 | 86 ± 34 | −1.3 ± 6.2 | −1.4 ± 6.9 |

Patients under dialysis, with renal transplantation, were excluded from calculations. Under exclusion of patients with hyperfiltration (>120 mL/min/1.73 $m^2$ on the basis of $eGFR_{creat}$) statistical results did not differ. Slopes of eGFR (annual percentage change) were calculated with the respective eGFR formula. Differences between groups have been tested using one-way ANOVA with post hoc (Ryan–Einot–Gabriel–Welsch) analysis. LTFU, long-term follow-up.

[a]$P < 0.05$ for baseline versus first follow-up.

[b]$P < 0.05$ for first versus second follow-up.

[c]$P < 0.05$ for regular-dose versus switch group.

[d]$P < 0.05$ for regular-dose versus re-switch group.

[e]$P < 0.05$ for switch versus re-switch group.

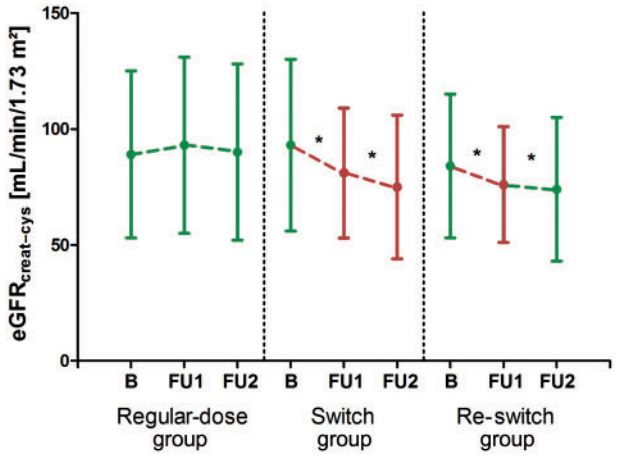


**FIGURE 2:** Changes of the creatinine-cystatine-based estimated GFR ($eGFR_{creat-cys}$) in the different treatment groups over time. Red bars: patients treated with agalsidase-alfa for least 12 months. Green bars: patients treated with agalsidase-beta for least 12 months. Values are presented as mean ± SD. FU, follow-up. *$P < 0.05$.

**Table 5. Outcome for cardiac parameters**

| Groups | Baseline | LTFU 1 | LTFU 2 |
|---|---|---|---|
| Regular-dose group ($n = 37$) | | | |
| LVSd, mm | 12.7 ± 3.0 | 12.7 ± 3.3 | 12.8 ± 3.8 |
| LVEF, % | 63 ± 8 | 57 ± 15 | 58 ± 10 |
| ECG abnormalities, $n$ (%) | 9 (24) | 13 (35) | 14 (38) |
| Switch group ($n = 38$) | | | |
| LVSd, mm | 13.2 ± 3.2 | 12.8 ± 3.1 | 13.4 ± 3.4 |
| LVEF, % | 65 ± 7 | 61 ± 7 | 62 ± 8 |
| ECG abnormalities, $n$ (%) | 12 (32) | 15 (39) | 18 (47) |
| Re-switch group ($n = 37$) | | | |
| LVSd, mm | 13.1 ± 3.2 | 12.8 ± 3.8 | 13.5 ± 3.4 |
| LVEF, % | 62 ± 5 | 58 ± 7 | 60 ± 9 |
| ECG abnormalities, $n$ (%) | 7 (19) | 9 (24) | 10 (27) |

Values are given as $n$ (%) or as mean ± SD. Differences between baseline and first/second long-term follow-up have been tested using Fisher's exact test. ECG, electrocardiogram; LTFU, long-term follow-up; LVEF, left ventricular ejection fraction; LVSd, left ventricular septum thickness in diastole.

($P < 0.05$) after 12 months stable on agalsidase-beta (RR 0.42; 95% CI 0.19–0.93; $P < 0.05$). There were no differences with respect to pain attacks or permanent pain. MSSI score, as a marker for general disease severity, showed an increase in the switch and re-switch groups until the first follow-up ($P < 0.05$), while the MSSI score in the regular dose group remained stable. Between the first and the second long-term follow-up, MSSI score remained stable across groups (Table 6).

## Outcome for clinical events

Increasing frequencies for implanted pacemakers between baseline examination and second follow-up were observed across treatment groups, while the resulting relative risks were only significant in the switch (RR 1.98; 95% CI 1.39–2.81; $P < 0.05$) and re-switch groups (RR 1.77; 95% CI 1.17–2.66; $P < 0.05$). There were no differences with respect to kidney transplantation or dialysis (Table 7).

The regular-dose and the switch groups showed decreasing frequencies of stroke/TIA between baseline and the second follow-up (both $P < 0.05$; Table 7), while the re-switch group firstly demonstrated a significant increase during the first long-term follow-up ($P < 0.05$) and a subsequent decrease until the second long-term follow-up ($P < 0.05$) with a comparable frequency to baseline (Table 7).

In general, relative risk for stroke/TIA was lower in the regular-dose group (RR 0.20; 95% CI 0.03–0.29; $P < 0.05$) and the switch group (RR 0.17; 95% CI 0.01–0.42; $P < 0.05$; Table 7) over time.

Two female patients (66 and 74 years of age) died due to stroke with subsequent sepsis and cardiac decompensation with

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**Table 6. Outcome for clinical symptoms**

| Groups | Baseline | LTFU 1 | LTFU 2 | RR (95% CI) |
|---|---|---|---|---|
| Regular-dose group ($n = 37$) | | | | |
| Abdominal pain, *n* (%) | 9 (24) | 11 (30) | 14 (38) | 1.05 (0.40–1.23) |
| Pain attacks, *n* (%) | 4 (11) | 4 (11) | 3 (8.1) | 1.16 (0.58–2.30) |
| Permanent pain, *n* (%) | 17 (46) | 18 (49) | 16 (43) | 0.95 (0.59–1.50) |
| Diarrhoea, *n* (%) | 12 (32) | 12 (32) | 14 (38) | 1.12 (0.71–1.78) |
| MSSI, score | 23 ± 12 | 25 ± 13 | 27 ± 12 | – |
| Switch group ($n = 38$) | | | | |
| Abdominal pain, *n* (%) | 3 (7.9)[a,c] | 7 (18)[b] | 13 (34) | 1.95 (1.33–2.85)[d] |
| Pain attacks, *n* (%) | 6 (16) | 4 (11) | 3 (7.9) | 0.65 (0.25–1.68) |
| Permanent pain, *n* (%) | 17 (46) | 15 (41) | 18 (47) | 1.05 (0.67–1.65) |
| Diarrhoea, *n* (%) | 6 (16)[a] | 12 (32) | 10 (26) | 1.34 (0.84–2.10) |
| MSSI, score | 19 ± 11[a] | 23 ± 12 | 25 ± 12 | – |
| Re-switch group ($n = 37$) | | | | |
| Abdominal pain, *n* (%) | 6 (16)[a,c] | 12 (32) | 14 (38) | 1.64 (1.08–2.51)[d] |
| Pain attacks, *n* (%) | 8 (22) | 5 (14) | 6 (16) | 0.83 (0.43–1.59) |
| Permanent pain, *n* (%) | 19 (51) | 20 (54) | 18 (49) | 0.95 (0.60–1.49) |
| Diarrhoea, *n* (%) | 15 (41)[c] | 13 (35)[b] | 5 (13) | 0.42 (0.19–0.93)[d] |
| MSSI, score | 16 ± 9[a] | 21 ± 10 | 22 ± 11 | – |

Values are given as *n* (%) or as mean ± SD. Differences between baseline and first/second long-term follow-up have been tested using Fisher's exact test. RR was calculated as odds ratio comparing baseline and second follow-up examination. LTFU, long-term follow-up.
[a]$P < 0.05$ for baseline versus first follow-up.
[b]$P < 0.05$ first follow-up versus second follow-up.
[c]$P < 0.05$ for baseline versus second follow-up.
[d]$P < 0.05$ for relative risk calculation.

**Table 7. Outcome for clinical events**

| Groups | Cumulative events until baseline | Cumulative events until first long-term follow-up | Events in so far unaffected patients | Cumulative events until second long-term follow-up | Events in so far unaffected patients | RR (95% CI) |
|---|---|---|---|---|---|---|
| Regular-dose group ($n = 37$) | | | | | | |
| Dialysis, *n* (%) | 9 (24) | 8 (22) | 0 | 9 (24) | 1 | 1.00 (0.35–2.98) |
| Kidney transplantation, *n* (%) | 3 (8.1) | 4 (11) | 1 | 4 (11) | 0 | 1.16 (0.58–2.30) |
| Pacemaker/ICD, *n* (%) | 3 (8.1)[a,c] | 7 (19) | 4 | 8 (22) | 1 | 1.58 (0.99–2.48) |
| TIA/strokes, *n* (%) | 8 (22)[c] | 3 (8.1) | 1 | 1 (2.7) | 1 | 0.20 (0.03–0.29)[d] |
| Switch group ($n = 38$) | | | | | | |
| Dialysis, *n* (%) | 6 (16) | 5 (13) | 0 | 5 (13) | 0 | 0.89 (0.45–1.79) |
| Kidney transplantation, *n* (%) | 3 (7.9) | 5 (13) | 2 | 5 (13) | 0 | 1.29 (0.71–2.3) |
| Pacemaker/ICD, *n* (%) | 1 (2.6)[a,c] | 6 (16) | 5 | 8 (21) | 2 | 1.98 (1.39–2.81)[d] |
| TIA/strokes, *n* (%) | 5 (13)[c] | 2 (5.2) | 2 | 0 (0.0) | 0 | 0.17 (0.01–0.42)[d] |
| Re-switch group ($n = 37$) | | | | | | |
| Dialysis, *n* (%) | 3 (8.1) | 2 (5.4) | 0 | 2 (5.4) | 0 | 0.79 (0.26–2.36) |
| Kidney transplantation, *n* (%) | 4 (11) | 4 (11) | 0 | 4 (11) | 0 | 1.00 (0.23–4.33) |
| Pacemaker/ICD, *n* (%) | 2 (5.4)[a,c] | 7 (19)[b] | 5 | 8 (22) | 1 | 1.77 (1.17–2.66)[d] |
| TIA/strokes, *n* (%) | 2 (5.4)[a] | 5 (14)[b] | 3 | 2 (5.4) | 2 | 1.00 (0.13–7.50) |

Values are given as *n* (%). Dialysis, kidney transplantation and pacemaker/ICD are given as number of patients (*n*) with event since last follow-up. TIA/strokes (events can occur more than once) are given as number of events (*n*) since last examination. ICD, implanted cardioverter defibrillator.
[a]$P < 0.05$ for baseline versus first follow-up.
[b]$P < 0.05$ first follow-up versus second follow-up.
[c]$P < 0.05$ for baseline versus second follow-up.
[d]$P < 0.05$ for relative risk.

infection-triggered chronic obstructive lung disease during the study and were treated with agalsidase-alfa in the switch and the re-switch group, respectively. Their last available data (before death) were implemented for the second long-term follow-up.

### Outcome for plasma lyso-Gb3

Plasma lyso-Gb3 levels were determined together with routine blood examination only at both long-term follow-up visits. Patients in the switch group had highest lyso-Gb3-values at the first long-term follow-up examination (26.7 ± 34.4 ng/mL), compared with the re-switch (17.5 ± 15.8 ng/mL; $P < 0.05$) and the regular-dose group (18.9 ± 15.2 ng/mL; $P < 0.05$). While the values remained stable in the regular-dose (18.4 ± 16.6 ng/mL; $P = 0.48$) and the switch groups (26.6 ± 28.4 ng/mL; $P = 0.97$), patients in the re-switch group showed a significant reduction of lyso-Gb3 (11.7 ± 13.1 ng/mL; $P < 0.05$) between the first and second long-term follow-up (Figure 3).

## DISCUSSION

During the agalsidase-beta supply shortage between 2009 and 2012, physicians were forced either to treat Fabry patients with



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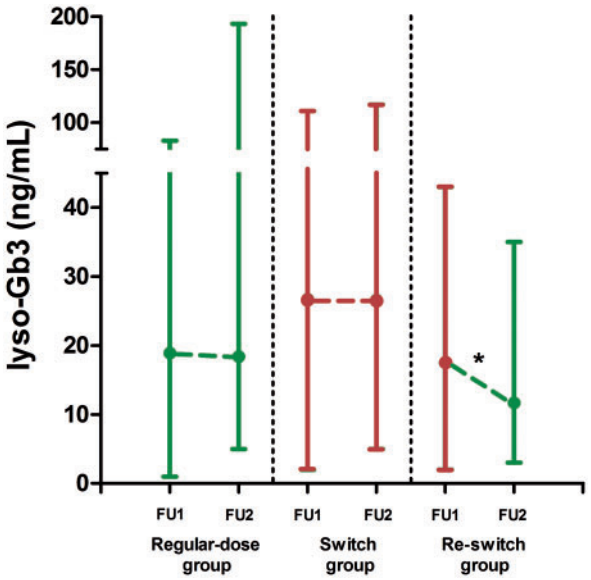


**FIGURE 3:** Plasma lyso-Gb3 values in the different treatment groups at follow-up examinations. Red bars: patients treated with agalsidase-alfa for at least 12 months. Green bars: patients treated with agalsidase-beta for least 12 months. Values are presented as median (quartiles). FU, follow-up. *$P < 0.05$.

a reduced dose of agalsidase-beta or to switch them to a regular dose of agalsidase-alfa. In our two prior observational studies, we demonstrated that patients receiving regular agalsidase-beta doses had a relatively stable disease course, but both dose reduction of agalsidase-beta and switch to agalsidase-alfa resulted in a decline of eGFR and deterioration of Fabry-related symptoms [7, 8]. Since 2013, some of these FD patients were re-switched to agalsidase-beta (full dose) as it became sufficiently available. Thus, in the current study, we assessed clinical stability, safety and outcome after re-switch to agalsidase-beta regular dose after 53 months of observation with special focus on clinical events, renal end-organ damage, disease-related clinical symptoms as well as disease severity.

Our main findings are: (i) irrespective of the ERT regime, FD patients generally showed a stable long-term disease course with respect to serious clinical events; (ii) FD patients after switch to agalsidase-alfa showed a continuous decline in eGFR, a higher frequency of gastrointestinal symptoms and an increase in plasma lyso-Gb3; and (iii) in patients who were re-switched from agalsidase-alfa to agalsidase-beta, the eGFR loss was attenuated and lyso-Gb3 levels ameliorated.

Randomized controlled trials and observational clinical studies with agalsidase-beta and agalsidase-alfa have shown that ERT is safe and efficient for treatment of patients with FD [7–10]. Initially, ERT compounds and dosages usually remained unchanged over time after ERT initiation. However, due to a viral contamination in 2009, the worldwide agalsidase-beta supply was limited and thus many patients were treated with a reduced dose of agalsidase-beta and/or were switched to agalsidase-alfa. Both therapy regimes were well tolerated in the context of infusion reactions and development of clinical events, but patients more often developed Fabry-related symptoms and presented with a decline of eGFR [6–8]. Because of the clinical experience in the Fabry centres and results of clinical observational studies, some FD patients were re-switched to agalsidase-beta after the restoration of the agalsidase-beta supply in 2013. The current study especially focused on these re-switched patients by clinical observation of organ function, Fabry-related symptoms and assessment of biomarkers (i.e. plasma lyso-Gb3). Due to the outcome results of our previous observational studies, eGFR was a special clinical target. In this context, one of the major findings was that the decline of eGFR and the increased occurrence of Fabry-related symptoms after switch to agalsidase-alfa could not be completely normalized but ameliorated after re-switch to agalsidase-beta.

In detail, the re-switch seemed to have three effects (impact on eGFR, gastrointestinal symptoms and lyso-Gb3) after 12 months of stable treatment with agalsidase-beta. First, a positive effect on eGFR was observed, i.e. the adverse decline of eGFR was attenuated, which was documented by the fact that the annual eGFR loss was slowed down (independent of the eGFR formula used) to $-2.2 \pm 4.4$ mL/min/1.73 m$^2$ ($eGFR_{creat-cys}$). Fabry nephropathy is a clinically relevant organ manifestation in FD and progressive eGFR loss leads to end-stage renal disease in the third to fifth decade of life [25, 26]. Cardiovascular outcomes in FD are linked to severity of CKD [27, 28]. The presence of end-stage renal disease is strongly associated with cardiovascular disease progression in Fabry patients. Since eGFR is one of the most important determinants of the clinical outcome in Fabry patients, GFR has to be regularly determined to assess kidney function. The KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [29] recommends use of the 2009 CKD-EPI equation to determine $eGFR_{creat}$ and suggest using the 2012 CKD-EPI equations to estimate GFR by $eGFR_{cys}$ or $eGFR_{creat-cys}$ whenever cystatin C is available. The equation that combines creatinine and cystatin C provides the most precise estimate of eGFR across all eGFR values [19].

Recently, Sirrs *et al.* [30] reported that no differences in events (renal/cardiac/cerebral) between agalsidase-alfa (0.2 mg/kg e.o.w.) and agalsidase-beta (1.0 mg/kg e.o.w.) have been observed within 5 years of treatment. However, although a head-to-head study, patients were randomized on gender only, but not for other variables such as proteinuria [31] and eGFR [28] at ERT-naïve baseline, which are known to affect prognosis. In addition, an effect of inhibitory antibody formation [24] or certain GLA mutations (i.e. late-onset variants) could not be fully excluded. By contrast, in our study, patients serve as their own controls in that all patients started with agalsidase-beta, which allows analysis of the individual impact of treatment changes. Since only six patients in our cohort presented with a mild or late-onset phenotype and were equally distributed across groups, an impact of mutation distribution on the outcome of the study seems unlikely.

Our results of a stable glomerular filtration in the regular-dose group on agalsidase-beta, and a progressive decline in the switch group on agalsidase-alfa with annual loss of $6.0 \pm 5.1$ and subsequently $4.6 \pm 9.1$ mL/min/1.73 m$^2$ (first and second long-term follow-up), as well as the amelioration in the re-switch group on agalsidase-beta with an attenuated annual loss

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of 2.2 ± 4.4 mL/min/1.73 $m^2$ (second long-term follow-up) compared with the preceding period on agalsidase-alfa with a more pronounced eGFR decline (−4.6 ± 9.1 mL/min/1.73 $m^2$/year) may be the clinical consequence of a dose-dependent clearance of the podocytes. Since podocytes lost their ability for mitosis, a replacement of disappeared cells is excluded. Therefore, podocytes play a pivotal role in nephropathy progression [32] and clearance of Gb3 inclusions decreases podocyte effacement, indicating a relationship between Gb3 inclusions and cellular structure/function [15, 16]. Skrunes *et al.* [16, 17] demonstrated a sustained long-term dose-dependent effect of Gb3 clearance of podocytes with more effective clearance on high-dose agalsidase (agalsidase-beta regular dose and agalsidase-alfa double dose) on the podocyte inclusions compared with the low-dose group (agalsidase-alfa regular dose). In detail, after Gb3 clearance of podocytes on agalsidase-beta (1.0 mg/kg BW e.o.w.), re-accumulation of Gb3 in podocytes occurred after 3 years of agalsidase-alfa (0.2 mg/kg e.o.w.) treatment. Subsequent reduction of podocyte Gb3 was observed in the single patient re-biopsied 2 years after re-switch to regular agalsidase-beta [17]. These data underline the importance of agalsidase dose for renal protection. A plausibility for a better effect of agalsidase-beta over agalsidase-alfa might be that agalsidase-alfa is prescribed at 5-fold lower dose than agalsidase-beta, which seems to results in an up to 10-fold lower intracellular agalsidase activity [33]. This hypothesis is underlined by renal biopsies demonstrating a long-term dose-dependent effect of Gb3 clearance of podocytes at least in young patients [17]. In addition, a higher agalsidase dose was associated with a better endothelial (but not medial) clearing of Gb3 in the vasculature, indicating that the higher the dose, the better the effect on extraglomerular vessels (in addition to the dose-dependent effect on clearing of podocyte Gb3, which also was sustained for 9 years) [17]. While some patients clearly demonstrate a dose-dependent effect on (measured) GFR, 'high-risk' patients predominantly treated with higher enzyme doses still might have a greater long-term decline in GFR. However, effects of different mannose residual patterns on both enzymes, which might affect cellular uptake by mannose-phosphate receptors, cannot be fully excluded. In conclusion, this study demonstrates that (at least) young patients treated up to 10 years need to be assessed individually in terms of risk progression [17].

In contrast to our findings after 1-year follow-up [7], ACR values did not differ between baseline and first as well as second long-term follow-up in any of the three groups. These results have to be interpreted with caution since the ACR values might be influenced by several factors such as glycaemic and blood pressure control, treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, nondihydropyridine calcium channel blockers (diltiazem and verapamil), salt consumption, exercise in the 24 h before the measurement, day time of the measurement and muscle mass (overestimated albumin excretion in a cachectic patient in whom muscle mass and creatinine excretion are markedly reduced) [34, 35].

Secondly, there was a positive effect on gastrointestinal symptoms: the current data document that after re-switching to agalsidase-beta, the frequency of the typical Fabry-related diarrhoea decreased. This effect is important as in the period of reduced dose of agalsidase-beta or switch to agalsidase-alfa many patients suffered from gastrointestinal symptoms. Thus, increasing the dose of ERT to 1.0 mg/kg BW e.o.w. may have had a positive effect on Fabry-typical gastrointestinal discomfort and pain.

Thirdly, a positive effect was seen on FD biomarker: it is well known that plasma Gb3 decreases significantly after ERT initiation and remains relatively stable. Lyso-Gb3 has emerged as a useful clinical biomarker of FD burden, with the possibility to identify clinical relevant agalsidase A mutations leading to FD [36]. The current study shows that at the two time points of long-term follow-up 1 and 2, lyso-Gb3 levels remained stable in the regular dose group and in the switch group as the dose of ERT was not changed in these two groups between the two time points. By contrast, lyso-Gb3 decreased in the re-switch group after increasing the dose from 0.2 mg/kg BW e.o.w. agalsidase-alfa to 1.0 mg/kg BW e.o.w. agalsidase-beta, indicating an amelioration of the disease burden. Although lyso-Gb3 levels were not available at the beginning of our study, the outcomes (stabilization of eGFR slopes and decrease of lyso-Gb3 levels within follow-up) are complementary to recent data from renal biopsies [16, 17]. Thus, as mentioned above, plasma lyso-Gb3 seems to be a reliable biomarker during ERT dose change, which parallels the change of eGFR and gastrointestinal symptoms. In fact, higher lyso-Gb3 values in the switch group could either be due to the lack of randomization or due to lower lyso-Gb3 response to agalsidase-alfa in general. In line with this assumption, Goker-Alpan *et al.* [37] as well as Skrunes *et al.* [17] recently demonstrated that lyso-Gb3 and intracellular Gb3 levels were reduced after switching from agalsidase-alfa to agalsidase-beta, indicating stronger pharmacodynamic effects at the higher dose, which also been suggested by a recent meta study [38]. Together with our results this might provide further evidence that lyso-Gb3 levels are dependent on agalasidase dose. However, as stated previously 38.5% of tested males presented with neutralizing anti-drug antibodies, a frequency that is in accordance with recent literature [24]. Since the prevalence for neutralizing anti-drug antibodies was comparable across the groups, we conclude that our results are independent of the appearance of inhibitory antibodies.

In accordance with our first two studies, the current data suggest that a switch from agalsidase-beta to agalsidase-alfa is generally safe. In addition, the re-switch to a regular agalsidase-beta dose did not result in clinically relevant infusion side reactions. Within the observation period, the subsequent re-switch to the high dose of agalsidase-beta was not able to fully reverse all of the observed clinical symptoms and events, but at least resulted in a stabilization of annual eGFR decline. In addition, a re-switch from agalsidase-alfa to agalsidase-beta resulted in decreased lyso-Gb3 levels, which has also recently been demonstrated for Gb3 inclusions in kidney biopsies [16] as well as plasma lyso-Gb3 levels during long-term follow-ups [17]. Due to the observational study design, it cannot be concluded that the regular agalsidase-beta dose regimen is the optimal treatment for all FD patients. According to the clinical differences between affected patients, we conclude that individual

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assessment of risk and therapy is mandatory in FD patients, and intensified surveillance is indicated in patients where dose reductions are undertaken.

### Limitations

A possible limitation of the current study is the observational nature and, therefore, an unavoidable selection of patients. In this 'real world scenario', patients were not randomized (and therefore the baseline data were not analysed between groups with adjustment) and thus outcomes of comparison between the three groups should be carefully interpreted. Hence, the current data cannot answer the question, which is the better compound and/or the optimal dose for ERT. Comparing data with a group starting and being consistent on agalsidase-alfa should be now the scope of future studies.

The total number of patients was slightly different from the initial publications [7, 8], since some patients switching the therapy regime more than twice during the follow-up were excluded and additional patients fulfilling the inclusion criteria were included. Due to the multicentre approach, some parameters and especially lyso-Gb3 levels as a potential marker for disease progression were not available for the entire study cohort. Even if we measured lyso-Gb3 at the first and second follow-up visit, the lack of lyso-Gb3 levels at baseline might be a limitation.


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## SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

## AUTHORS' CONTRIBUTIONS

All authors contributed to the research idea and study design; J.K., M.L., S.C.-K., P.N., N.Ü., D.B., T.D., S.R., J.S., T.G., C.W., C.S., E.B. and F.W. were responsible for data acquisition; J.K., M.L., S.C.-K., P.N., N.Ü., T.D., J.S., C.W., C.S., S.S., S.-M.B., E.B. and F.W. undertook data analysis/interpretation; J.K., M.L. and S.S. performed statistical analysis; and C.W., E.B. and F.W. provided supervision and mentorship. Each author contributed important intellectual content during manuscript drafting and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. E.B. and F.W. take responsibility that this study has been reported honestly, accurately and transparently, that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

## CONFLICT OF INTEREST STATEMENT

F.W., J.K., M.L., C.W., T.D., S.C.-K. and E.B. have received speaker honoraria from Genzyme and Shire Corporation. F.W. and C.W. are members of the Fabry Registry European Board of Advisors and have received travel assistance and speaker honoraria. Research grants were given to the institutions (Würzburg and Münster) by Genzyme and Shire Corporations. N.Ü. has received travel assistance and speaker honoraria from Genzyme Corporation and Shire Corporation. C.S. has received speaker honoraria from Genzyme Corporation. S.-M.B. has received speaker honoraria from Shire Corporation.

(See related article by Ortiz and Sanchez-Niño. Enzyme replacement therapy dose and Fabry nephropathy. *Nephrol Dial Transplant* 2018; 33: 1284–1289)

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