Supplemental Table 1: Overview of male patients under ERT at the time-point of ERT inhibition determination.

mutation	GLA activity (% reference)	lyso-GB3 (ng/ml)	ERT^{+}	initial analysis	ever pre-medication against infusion reactions	5-year retrospective	current ERT	switch of product prior to inhibition analysis	FD-typical symptoms and endorgan manifestations (renal/cardiac/neurologic)
p.G35E	4.0	13.0	0	1	0	0	α	no	CKD stage 1, albuminuria
p.L45P	0.0	63.4	0	1	0	1	α	no	CKD stage 1, LVH, arrhythmia, stroke
p.L45P	15.6	78.0	0	1	0	0	α	no	hyperfiltration, arrhythmia, NYHA I, neuropathic pain
p.C94S	9.4	21.3	0	1	1	1	α	yes, switch 48 months before analysis	CKD stage 1 LVH, NYHA I, neuropathic pain, recurrent strokes
p.C94S	22.5	na	1	1	0	0	β	no	CKD stage 4, dialysis, LVH, NYHA I, neuropathic pain
p.C94S	15.6	45.7	1	1	1	1	α	yes, re-switch, 14 months before analysis	CKD stage 1, LVH, NYHA I, neuropathic pain
p.A143T	50.0	0.7	0	1	0	0	β	no	hyperfiltration, family history of stroke
p.A143T	33.0	0.7	0	1	0	0	α	no	CKD stage 2, albuminuria, NYHA I, family history of stroke
p.W162C	12.5	35.4	0	1	0	0	α	no	CKD stage 2, albuminuria, LVH, ICD, NYHA II
p.W162G	6.3	40.0	0	1	0	0	α	no	CKD stage 2, albuminuria, LVH, NYHA I, neuropathic pain, stroke
p.D170N	12.5	22.7	0	1	0	1	β	yes, re-switch, 24 months before analysis	CKD stage 1, albuminuria, LVH, stroke
p.C172G	0.9	48.8	0	1	0	1	α	no	CKD stage 4, albuminuria, LVH, NYHA IV, stroke, recurrent TIAs, WML

p.Y173X	15.0	46.9	1	1	1	1	α	yes, switch, 13 months before analysis	CKD stage 5, dialysis, albuminuria, LVH, NYHA II, neuropathic pain
p.K213M	32.0	10.4	0	1	0	1	α	yes, switch 36 months before analysis	CKD stage 3, albuminuria, LVH, NYHA I, neuropathic pain
p.N215S	43.8	5.9	0	1	0	1	β	yes, re-switch, 24 months before analysis	CKD stage 3, LVH, atrial fibrillation, ICD, NYHA II, TIAs
p.N215S	4.0	3.7	0	1	0	1	α	yes, switch 36 months before analysis	CKD stage 1, NYHA II, ICD, LVH
p.R220X	7.3	na	0	1	0	0	α	no	CKD stage 2, albuminuria, LVH, NYHA I, recurrent strokes
p.R220X	16.0	107.0	1	1	0	1	α	yes, re-switch, 48 months before analysis	CKD stage 1, albuminuria, LVH, NYHA I neuropathic pain, recurrent strokes
p.R220X	12.5	59.8	1	1	0	1	β	yes, re-switch, 24 months before analysis	CKD stage 2, LVH, NYHA II neuropathic pain, WML, TIA
p.R220X	25.0	24.4	1	1	1	0	β	yes, re-switch, 12 months before analysis	CKD stage 1, LVH, NYHA I, neuropathic pain, recurrent TIAs
p.R220X	6.3	44.4	1	1	1	1	α	yes, switch, 30 months before analysis	CKD stage 3, albuminuria, NYHA III, neuropathic pain, stroke, recurrent TIAs
p.R220X	15.6	38.0	1	1	0	1	α	yes, switch, 35 months before analysis	CKD stage 1, albuminuria, neuropathic pain
p.R220X	20.0		1	1	0	0	α	yes, switch, 14 months before analysis	CKD stage 2, LVH, NYHA I, neuropathic pain, WML
p.H225D	5.6	8.6	1	1	1	0	α	no	CKD stage 5, dialysis, LVH, NYHA IV, WML

p.R227X	3.1	81.2	1	1	0	1	β	yes, switch, 12 months before analysis	CKD stage 4, albuminuria, LVH, NYHA I, neuropathic pain, WML
p.R227X	0.0	110.0	1	1	0	1	α	no	CKD stage 1, LVH, NYHA I, neuropathic pain
p.P259R	22.0	20.4	0	1	1	0	β	no	CKD stage 2, albuminuria, LVH, NYHA I
p.M267T	21.4	na	0	1	0	0	α	no	CKD stage 1, albuminuria, stroke
p.L294S	9.4	52.6	0	1	0	1	α	yes, switch 48 months before analysis	CKD stage 1, hyperfiltration, albuminuria, NYHA I, neuropathic pain, WML
p.L294S	12.5	26.9	1	1	0	1	β	no	CKD stage 1, NTX, LVH, NYHA II neuropathic pain, TIA
p.R301Q	8.5	18.9	1	1	0	0	α	no	CKD stage 3, albuminuria, LVH, NYHA II
p.G325S	22.5	6.7	0	1	0	1	α	yes, switch 36 months before analysis	CKD stage 3, albuminuria, LVH, NYHA I
p.Y365 CfsX5	25.0	55.0	1	1	0	0	α	no	CKD stage 5, dialysis, albuminuria, LVH, NYHA I, neuropathic pain
Exon 7, c1222 del A	6.3	28.4	0	1	0	0	β	yes, re-switch, 13 months before analysis	CKD stage 4, ICD, NYHA II, recurrent TIAs
Deletion Exon 7	2.0	29.9	1	1	0	1	β	no	CKD stage 2, albuminuria, LVH, NYHA I, neuropathic pain
c.762ins282bp		34.1	1	1	1	1	β	no	CKD stage 1, NYHA I, neuropathic pain, stroke, WML
IVS2+1 G>T	24.0	33.1	0	1	0	1	α	yes, switch 36 months before analysis	CKD stage 1, albuminuria, NYHA I, neuropathic pain
IVS2+1 G>T	3.1	29.0	0	1	0	0	α	no	CKD stage 1, hyperfiltration, albuminuria, NYHA I
IVS2+1 G>A	3.1	25.0	0	1	0	1	α	yes, switch 36 months before analysis	CKD stage 1, neuropathic pain

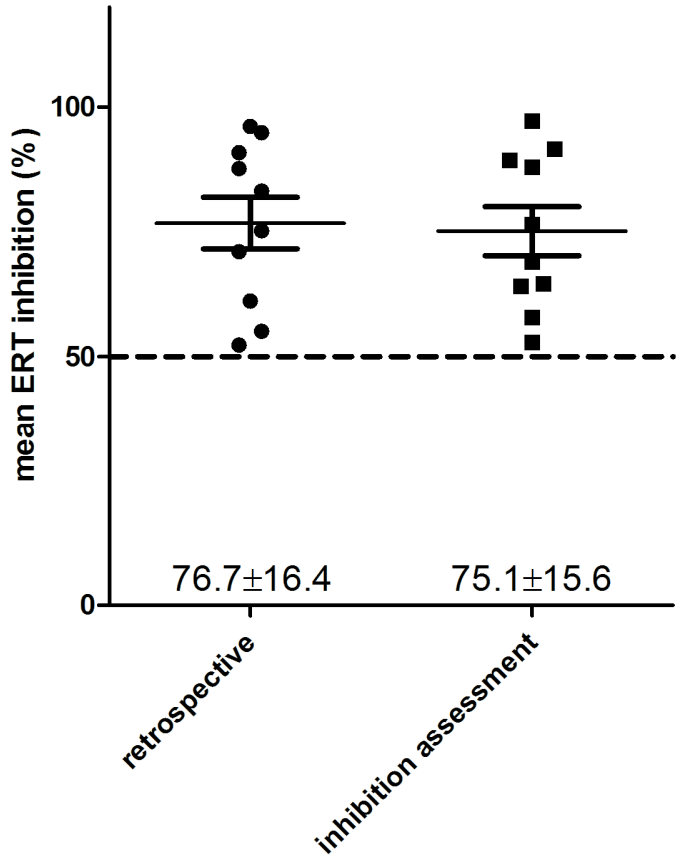
IVS2-2 A>G	25.0	46.9	1	1	1	1	α	no	CKD stage 1, NYHA II, neuropathic pain
IVS5+3 A>T	25.0	28.4	0	1	0	1	α	yes, switch 36 months before analysis	CKD stage 3, albuminuria, NYHA I

Missense mutations include single nucleotide exchanges, resulting in single aminoacid substitutions. Nonsense mutations include 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. Albuminuria is defined as an albumin/creatinine ratio >30 mg/g. Renal impairment was classified according to recent KDIGO guidelines. ERT: enzyme replacement therapy, LVH: left ventricular hypertrophy, NYHA: New York Heart Association; WML: white matter lesions; TIA: transient ischemic attack; α: agalsidase-alpha; β: agalsidase-beta. na: not available.

Supplemental table 2. . Multivariate regression analysis to assess the influence of serum-mediated ERT inhibition on cardiac and renal measures without correction for nonsense mutations.

measure	**ERT^{i-} (n=23)**	**ERT^{i+} (n=18)**	**p value**	**Δestimate**
LV_{mass}/BSA, g/m²	74.3±7.1	104.0±9.1	0.0204	29.7±12.1
RWT, cm	0.44±0.04	0.56±0.06	0.1149	0.12±0.07
eGFR, ml/min/1.73 m²	92.1±8.3	65.8±8.8	0.0207	-26.3±10.7

The mixed model approach for LVmass and RWT calculations was adjusted for age, duration of ERT, prescription of angiotensin aldosterone system blockers, body weight, systolic and diastolic blood pressure. The mixed model approach for eGFR calculation was adjusted for age, duration of ERT, the prescription of renin angiotensin aldosterone system blockers and diuretics. Patients with renal transplantation and hyperfiltration were excluded from calculations. Creatinine-based eGFR was calculated via Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula according to Levey et al. 2009.



Supplemental Figure 1

Retrospective inhibition measurements of 10 ERT^{i+} patients. Blood samples were obtained 1-2 years (retrospective) prior to inhibition status assessment and demonstrate that none of the analyzed patients changed his inhibition status between the measurements.