

Supplementary File

Supplementary Table 1 Characteristics by phenotype (analysis A: treatment time from onset of symptoms)

	Classical (n=242)			Late-onset (n=53)		
	Prompt (n=18)	Delayed (n=224)	P-value	Prompt (n=15)	Delayed (n=38)	P-value
Sex, n (%)						
N	18	224		15	38	
Male	10 (55.6)	128 (57.1)	0.896 ^a	13 (86.7)	29 (76.3)	0.403 ^a
Female	8 (44.4)	96 (42.9)		2 (13.3)	9 (23.7)	
Age at symptom onset, years						
N	18	224		15	38	
Mean (SD)	30.3 (15.2)	16.7 (13.9)	<0.001 ^b	54.4 (8.4)	43.7 (17.1)	0.025 ^b
Age at diagnosis, years						
N	18	221		15	38	
Mean (SD)	29.1 (16.9)	29.8 (16.6)	0.870 ^b	54.3 (8.5)	54.6 (14.9)	0.935 ^b
Age at treatment initiation, years						
N	18	224		15	38	
Mean (SD)	31.2 (15.4)	39.1 (14.8)	0.030 ^b	55.3 (8.7)	57.1 (13.9)	0.646 ^b
Symptom onset to treatment initiation, years						
N	18	224		15	38	
Mean (SD)	0.9 (0.5)	22.4 (13.1)	<0.001 ^b	0.9 (0.6)	13.4 (15.0)	0.002 ^b
Diagnosis to treatment initiation, years						
N	18	221		15	38	
Mean (SD)	2.1 (2.7)	9.3 (11.4)	0.008 ^b	1.0 (0.5)	2.5 (2.7)	0.047 ^b
Symptom onset to diagnosis, years						
N	18	221		15	38	
Mean (SD)	0.3 (0.5)	13.5 (13.4)	<0.001 ^b	0.1 (0.4)	11.2 (14.4)	0.005 ^b
eGFR at baseline, mL/min/1.73m ²						
N	13	142		13	30	
Mean (SD)	94.3 (31.2)	93.3 (30.6)	0.913 ^b	88.6 (10.5)	88.1 (21.2)	0.941 ^b
LVMI at baseline, g/m ^{2.7}						
N	5	88		8	18	
Mean (SD)	50.2 (14.5)	51.7 (16.7)	0.848 ^b	64.6 (25.5)	63.4 (26.0)	0.913 ^b

History of cardiovascular events						
N	18	224		15	38	
Yes, n (%)	4 (22.2)	125 (55.8)	0.006 ^a	11 (73.3)	30 (78.9)	0.660 ^a
History of renal events						
N	18	224		15	38	
Yes, n (%)	3 (16.7)	95 (42.4)	0.032 ^a	0	4 (10.5)	0.191 ^a
Family history						
N	17	207		14	36	
Yes, n (%)	15 (88.2)	194 (93.7)	0.384 ^a	12 (85.7)	31 (86.1)	0.971 ^a

The prompt treatment cohort initiated agalsidase alfa <24 months after symptom onset; the delayed treatment cohort initiated agalsidase alfa ≥24 months after symptom onset. Baseline was defined as the date closest to agalsidase alfa initiation within a window of –6 months to +3 months. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration. Values were restricted to 10–160 mL/min/1.73 m² for eGFR and 10–120 g/m^{2.7} for LVMI; values outside these ranges were considered missing. History of cardiovascular and/or renal events refers to respective events that occurred prior to or at the date of agalsidase alfa initiation. *P*-values were derived from ^aChi-square test and ^b*t* test.

Mutation classification was reported for patients both with genetic informed consent form and who provided genetic data.

Abbreviations: eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index.

Supplementary Table 2 Characteristics by phenotype (analysis B: treatment time from diagnosis)

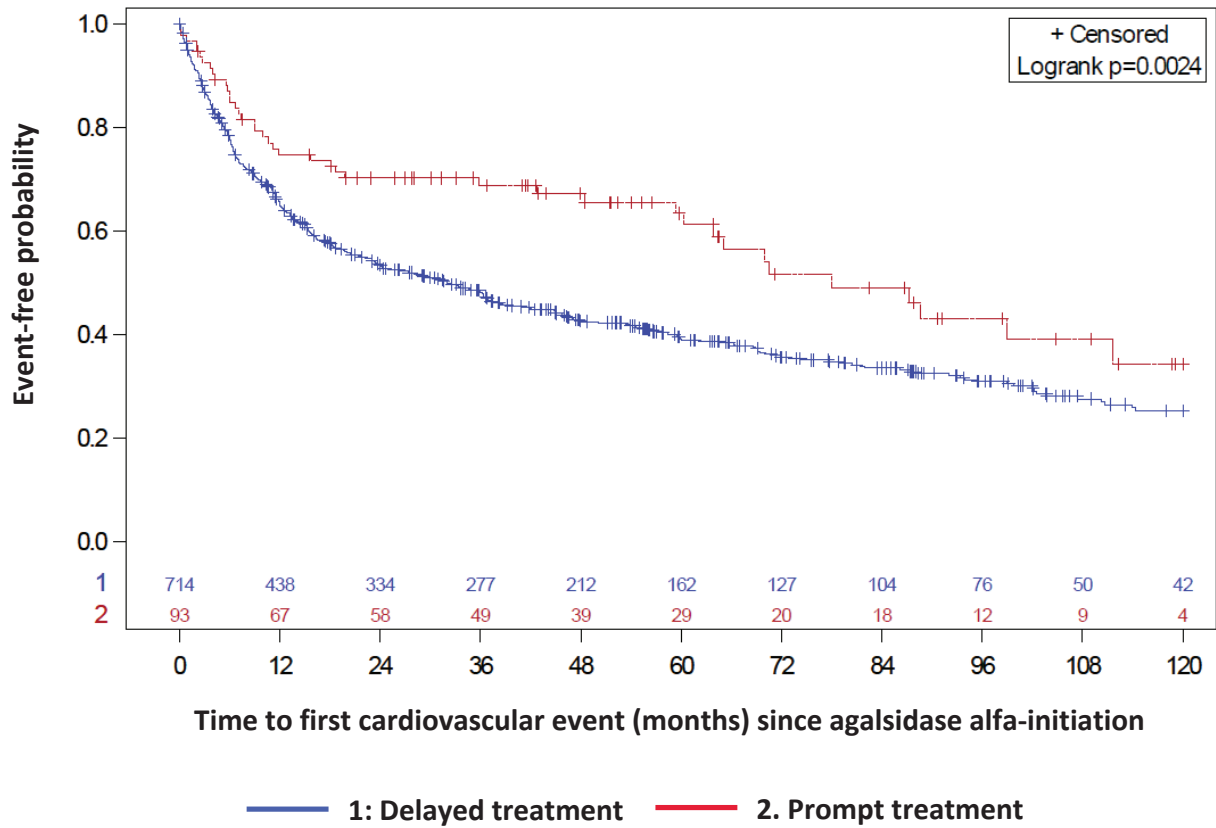
	Classical (n=349)			Late-onset (n=96)		
	Prompt (n=152)	Delayed (n=197)	<i>P</i> -value	Prompt (n=72)	Delayed (n=24)	<i>P</i> -value
Sex, n (%)						
N	152	197		72	24	
Male	82 (53.9)	97 (49.2)	0.383 ^a	59 (81.9)	16 (66.7)	0.117 ^a
Female	70 (46.1)	100 (50.8)		13 (18.1)	8 (33.3)	
Age at symptom onset, years						
N	102	137		38	15	
Mean (SD)	18.1 (14.3)	17.4 (14.6)	0.700 ^b	52.0 (9.2)	33.4 (21.1)	<0.001 ^b
Age at diagnosis, years						
N	152	197		72	24	
Mean (SD)	37.8 (15.7)	27.1 (16.9)	<0.001 ^b	57.8 (9.8)	45.5 (17.9)	<0.001 ^b
Age at treatment initiation, years						
N	152	197		72	24	
Mean (SD)	38.6 (15.8)	40.1 (15.9)	0.391 ^b	58.8 (9.8)	50.7 (17.3)	0.005 ^b
Symptom onset to treatment initiation, years						
N	102	137		38	15	
Mean (SD)	18.8 (14.5)	22.3 (13.3)	0.056 ^b	7.3 (8.2)	16.5 (21.7)	0.028 ^b
Diagnosis to treatment initiation, years						
N	152	197		72	24	
Mean (SD)	0.8 (0.5)	13.0 (11.2)	<0.001 ^b	1.0 (0.4)	5.1 (3.0)	<0.001 ^b
Symptom onset to diagnosis, years						
N	102	137		38	15	
Mean (SD)	18.0 (14.4)	8.4 (10.9)	<0.001 ^b	6.4 (8.1)	12.3 (20.9)	0.140 ^b
eGFR at baseline, mL/min/1.73m ²						
N	88	128		56	19	
Mean (SD)	92.3 (31.1)	95.4 (28.9)	0.453 ^b	81.9 (18.0)	94.8 (26.6)	0.021 ^b
LVMI at baseline, g/m ^{2.7}						
N	48	73		37	11	
Mean (SD)	52.8 (18.0)	50.1 (16.3)	0.386 ^b	63.9 (23.1)	52.8 (22.8)	0.168 ^b
History of cardiovascular events						
N	152	197		72	24	

Yes, n (%)	63 (41.4)	123 (62.4)	<0.001 ^a	58 (80.6)	18 (75.0)	0.562 ^a
History of renal events						
N	152	197		72	24	
Yes, n (%)	48 (31.6)	85 (43.1)	0.027 ^a	7 (9.7)	4 (16.7)	0.355 ^a
Family history						
N	145	175		69	22	
Yes, n (%)	132 (91.0)	164 (93.7)	0.365 ^a	61 (88.4)	20 (90.9)	0.744 ^a

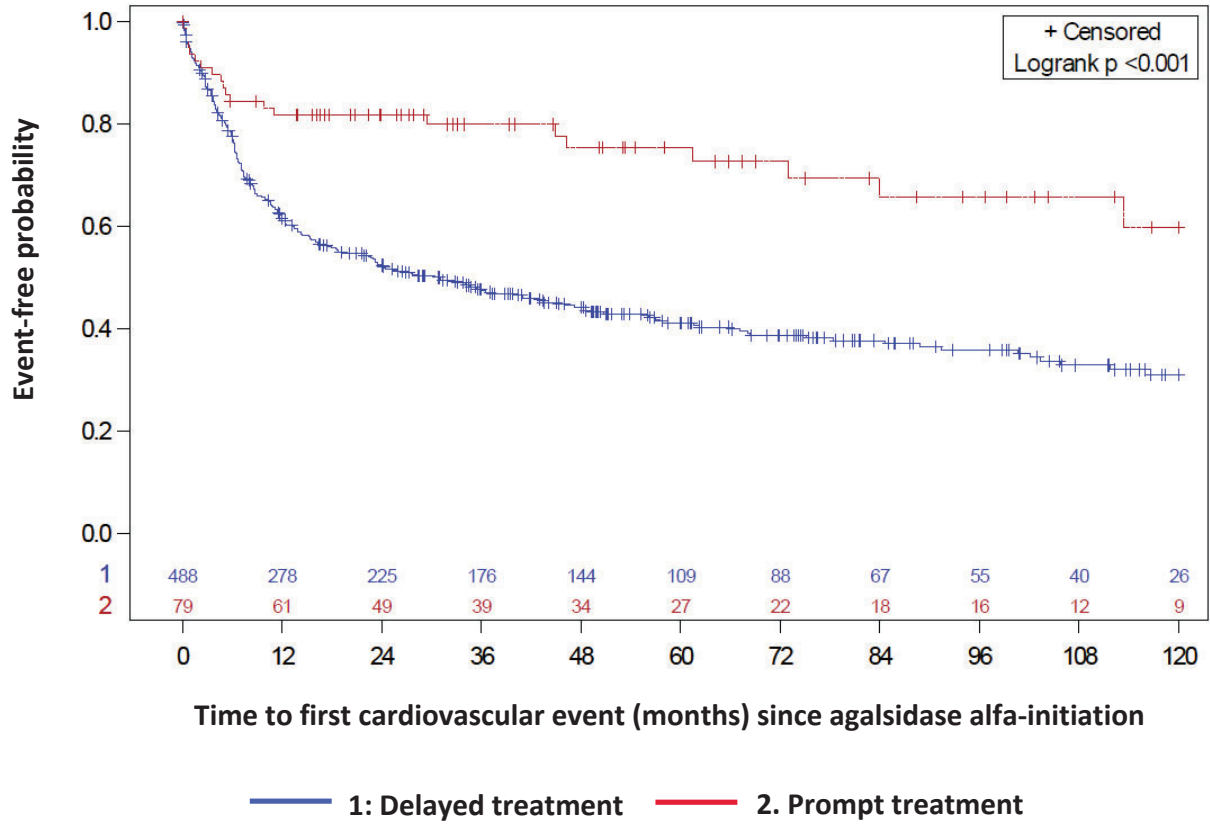
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Abbreviations: eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index.

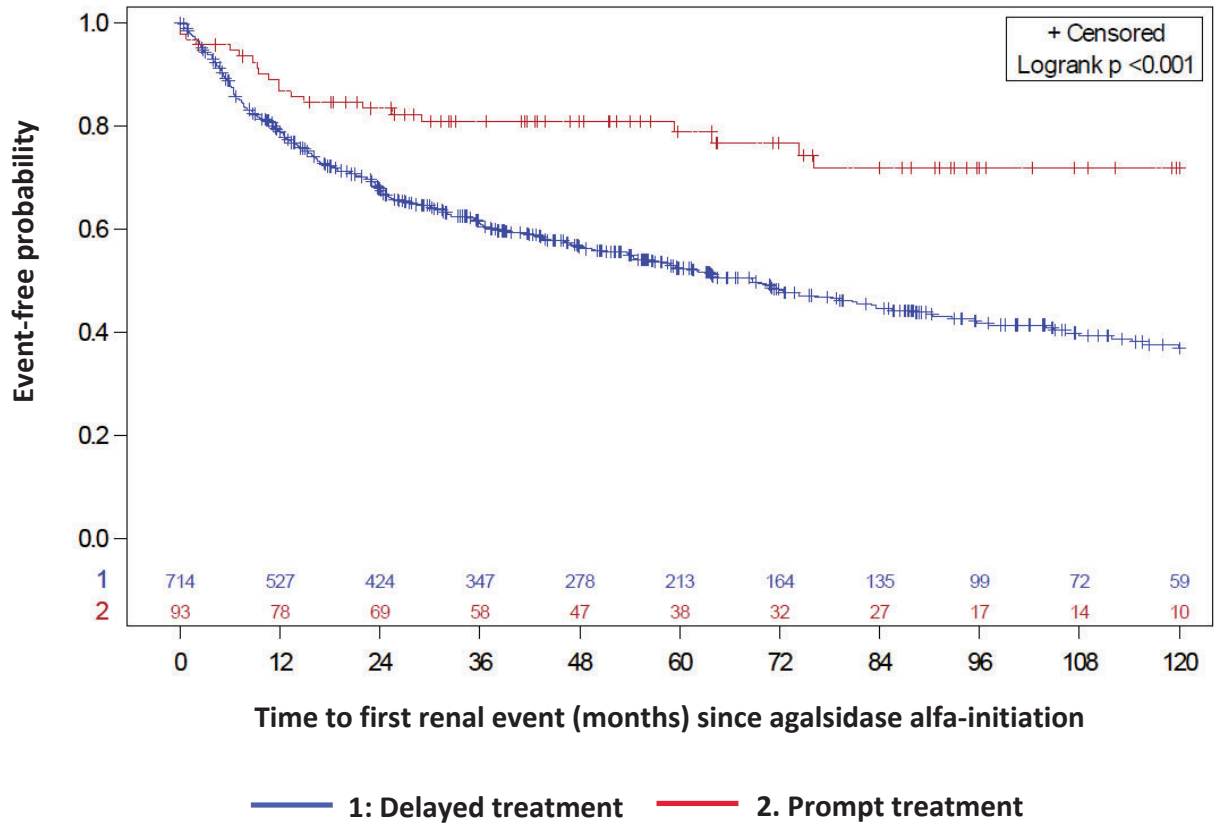
Supplemental Figure 1. Kaplan-Meier curves with log-rank test showing time to first cardiovascular event according to prompt/delayed agalsidase alfa initiation in male patients (analysis A: treatment time from onset of symptoms).



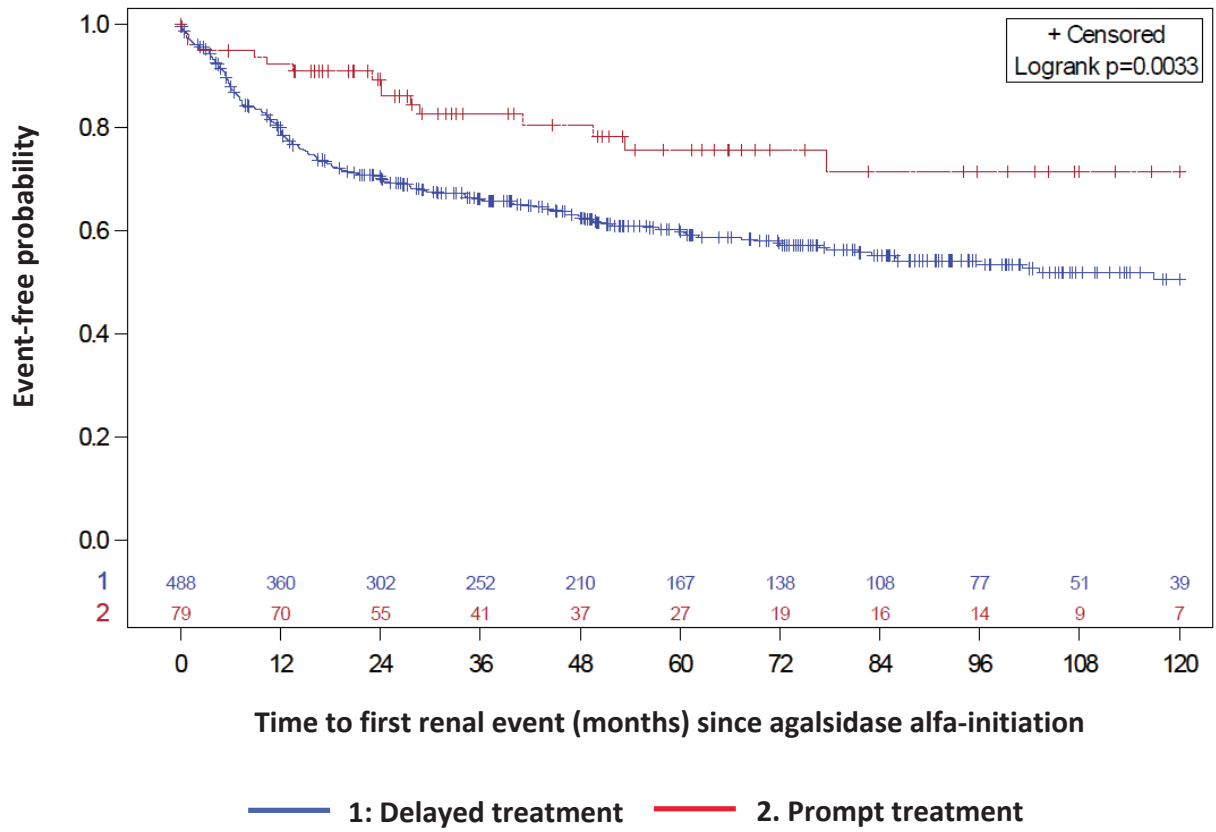
Supplemental Figure 2. Kaplan-Meier curves with log-rank test showing time to first cardiovascular event according to prompt/delayed agalsidase alfa initiation in female patients (analysis A: treatment time from onset of symptoms).



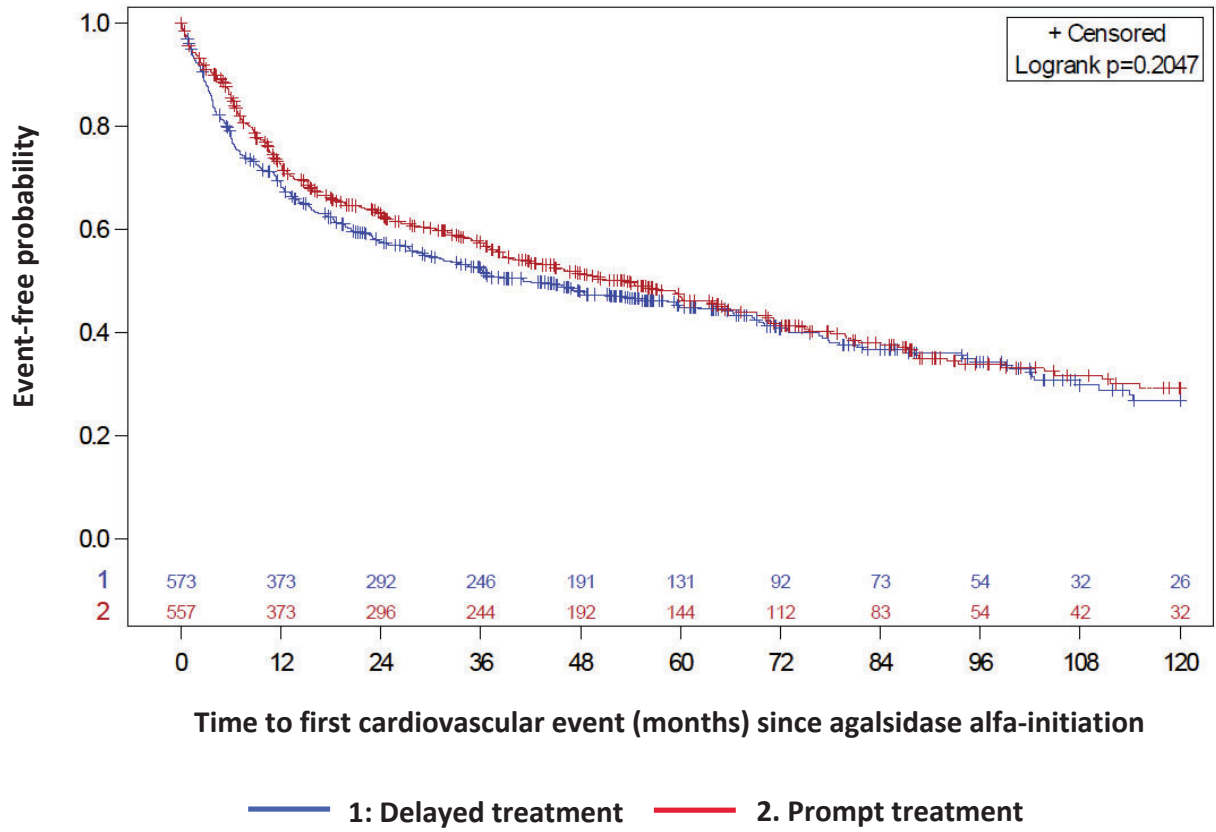
Supplemental Figure 3. Kaplan-Meier curves with log-rank test showing time to first renal event according to prompt/delayed agalsidase alfa initiation in male patients (analysis A: treatment time from onset of symptoms).



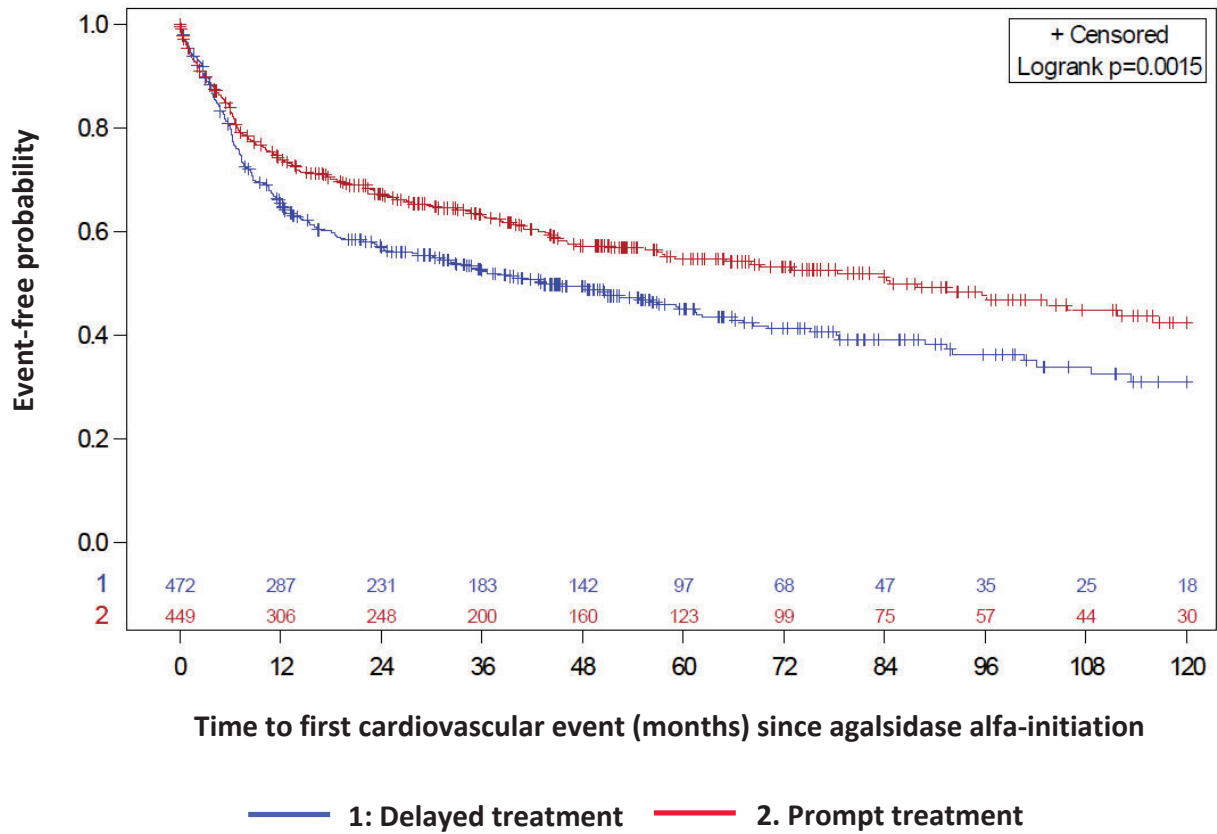
Supplemental Figure 4. Kaplan-Meier curves with log-rank test showing time to first renal event according to prompt/delayed agalsidase alfa initiation in female patients (analysis A: treatment time from onset of symptoms).



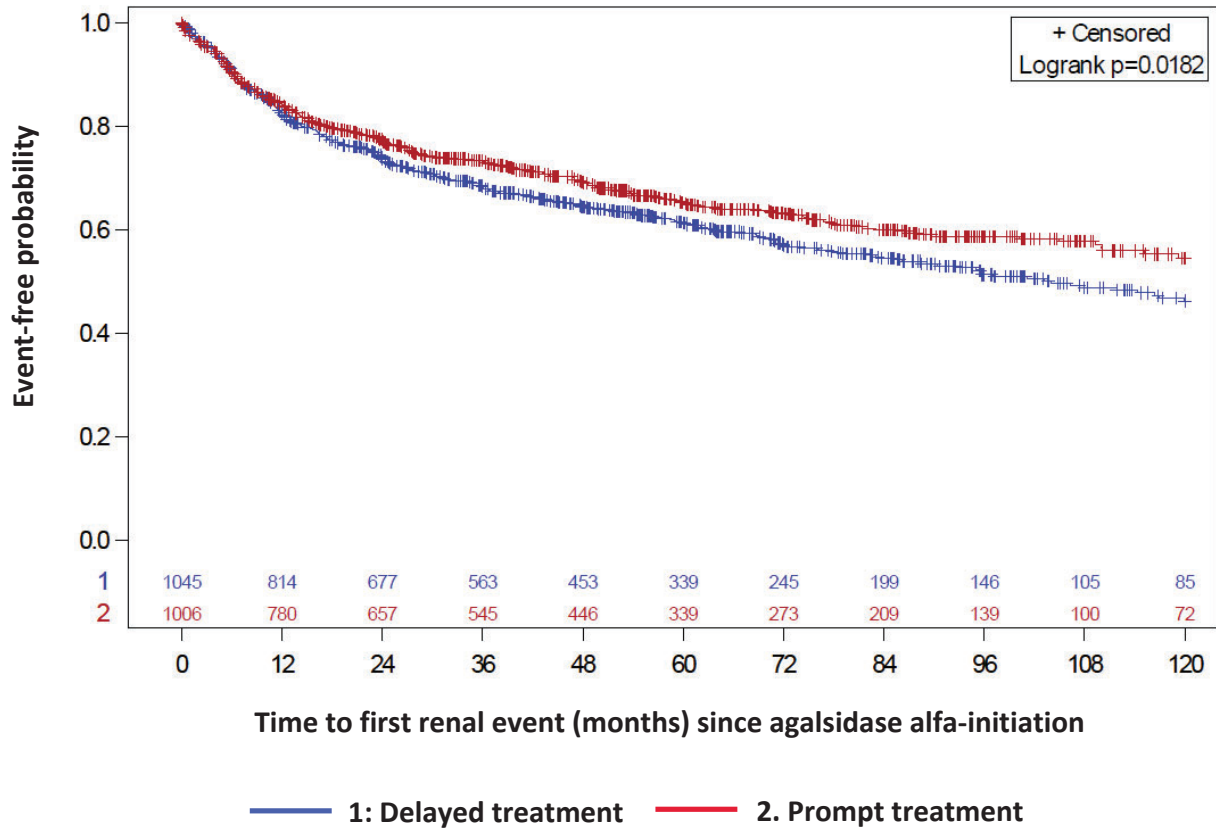
Supplemental Figure 5. Kaplan-Meier curves with log-rank test showing time to first cardiovascular event according to prompt/delayed agalsidase alfa initiation in male patients (analysis B: treatment time from diagnosis).



Supplemental Figure 6. Kaplan-Meier curves with log-rank test showing time to first cardiovascular event according to prompt/delayed agalsidase alfa initiation in female patients (analysis B: treatment time from diagnosis).



Supplemental Figure 7. Kaplan-Meier curves with log-rank test showing time to first renal event according to prompt/delayed agalsidase alfa initiation in male patients (analysis B: treatment time from diagnosis).



Supplemental Figure 8. Kaplan-Meier curves with log-rank test showing time to first renal event according to prompt/delayed agalsidase alfa initiation in female patients (analysis B: treatment time from diagnosis).

