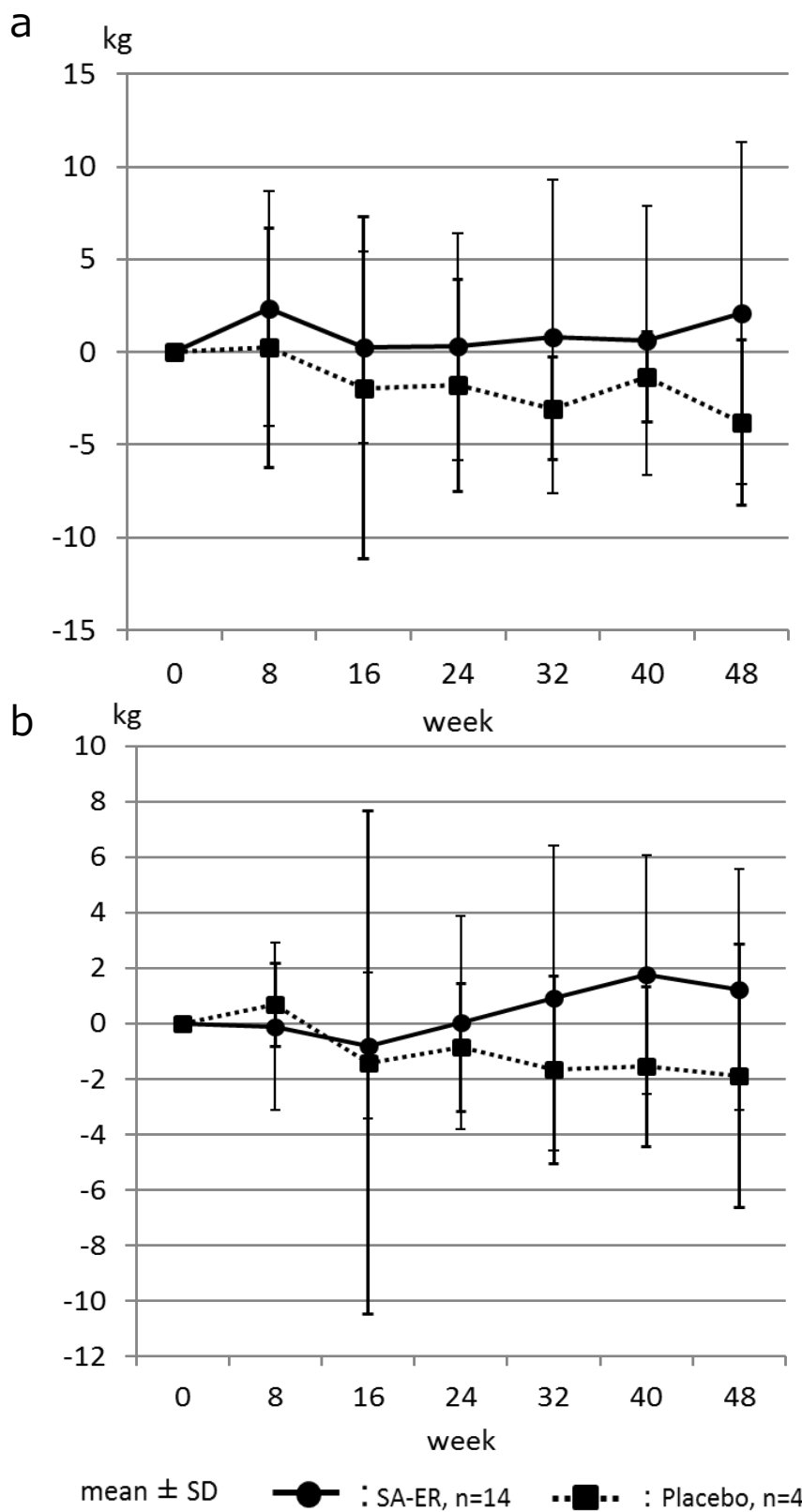
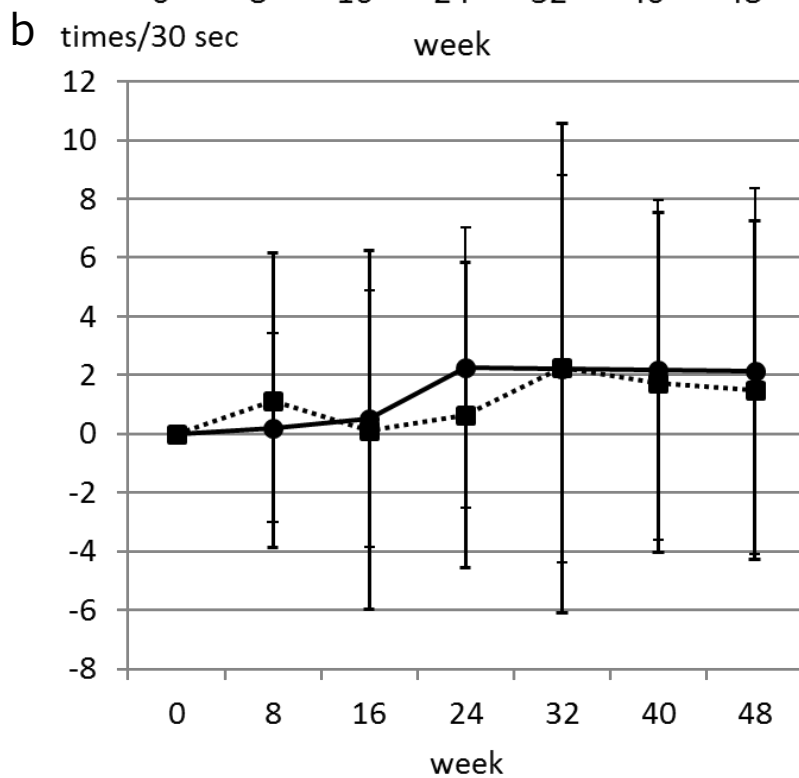
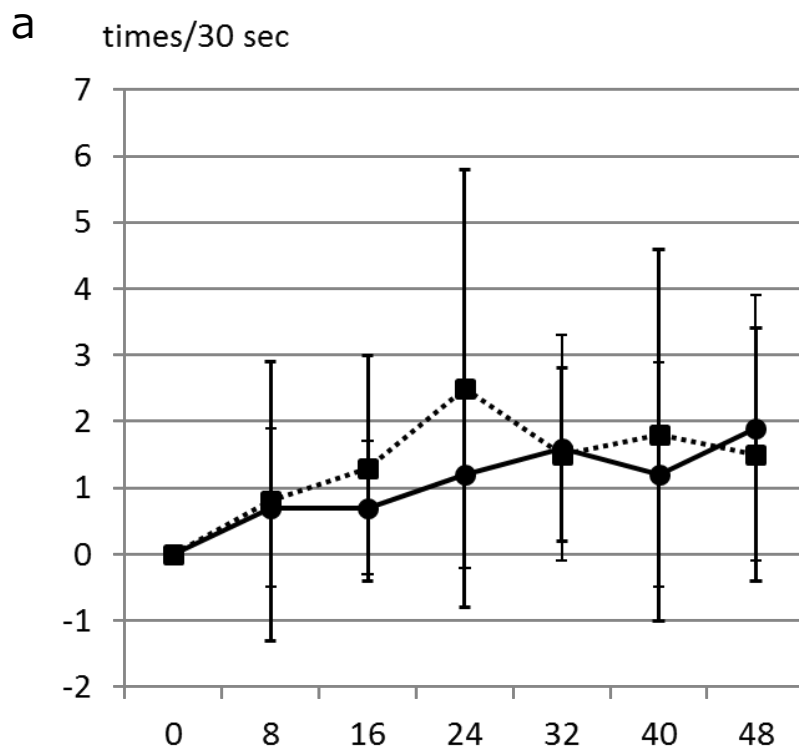


Supplementary Figure 1. Change in GNE myopathy functional activity score
a. upper extremity, b. mobility, c. self-care, d. total score



Supplementary Figure 2. Change in lower extremity composite score (a) and muscle strength of knee extensors (b)

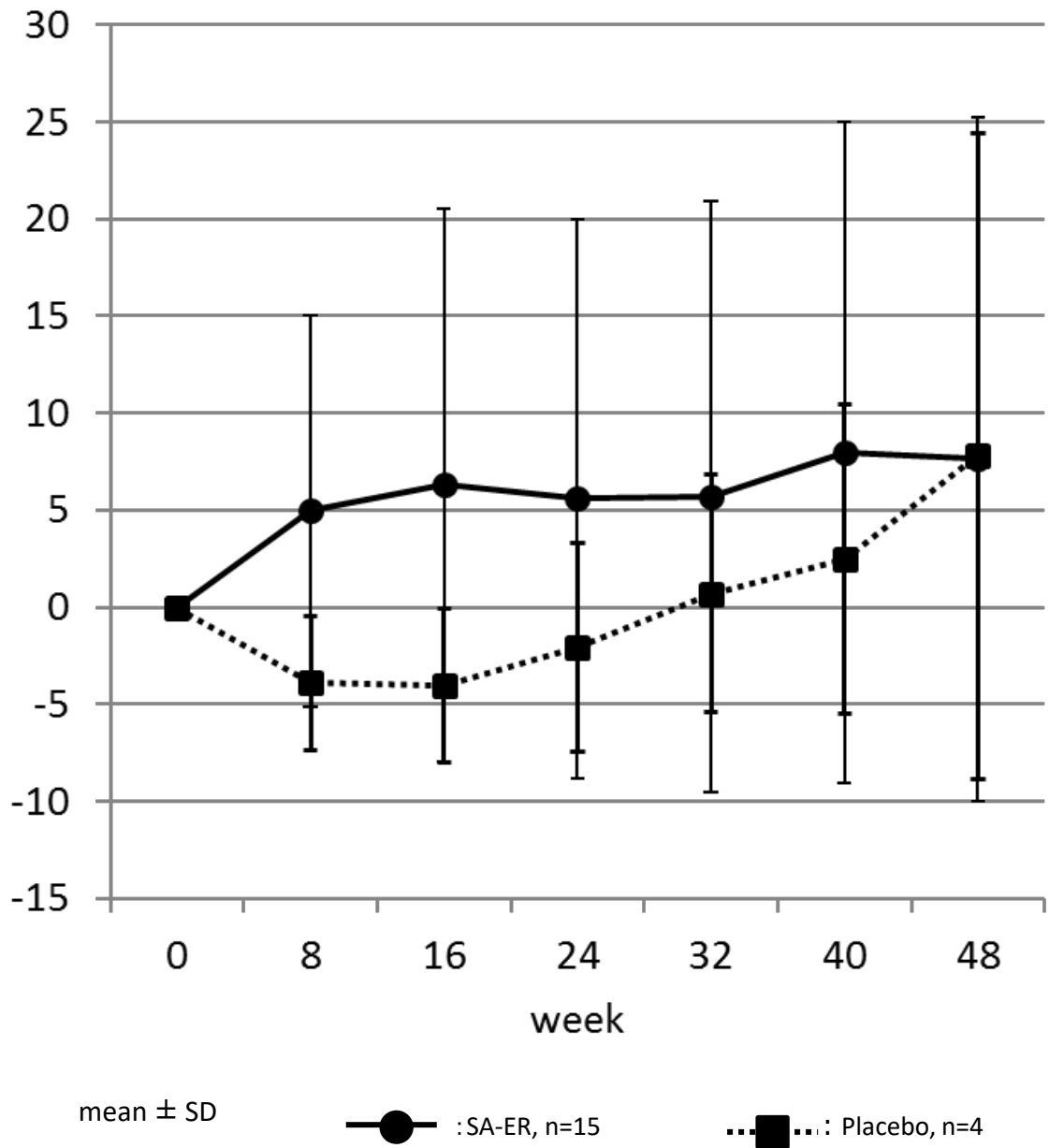


mean \pm SD

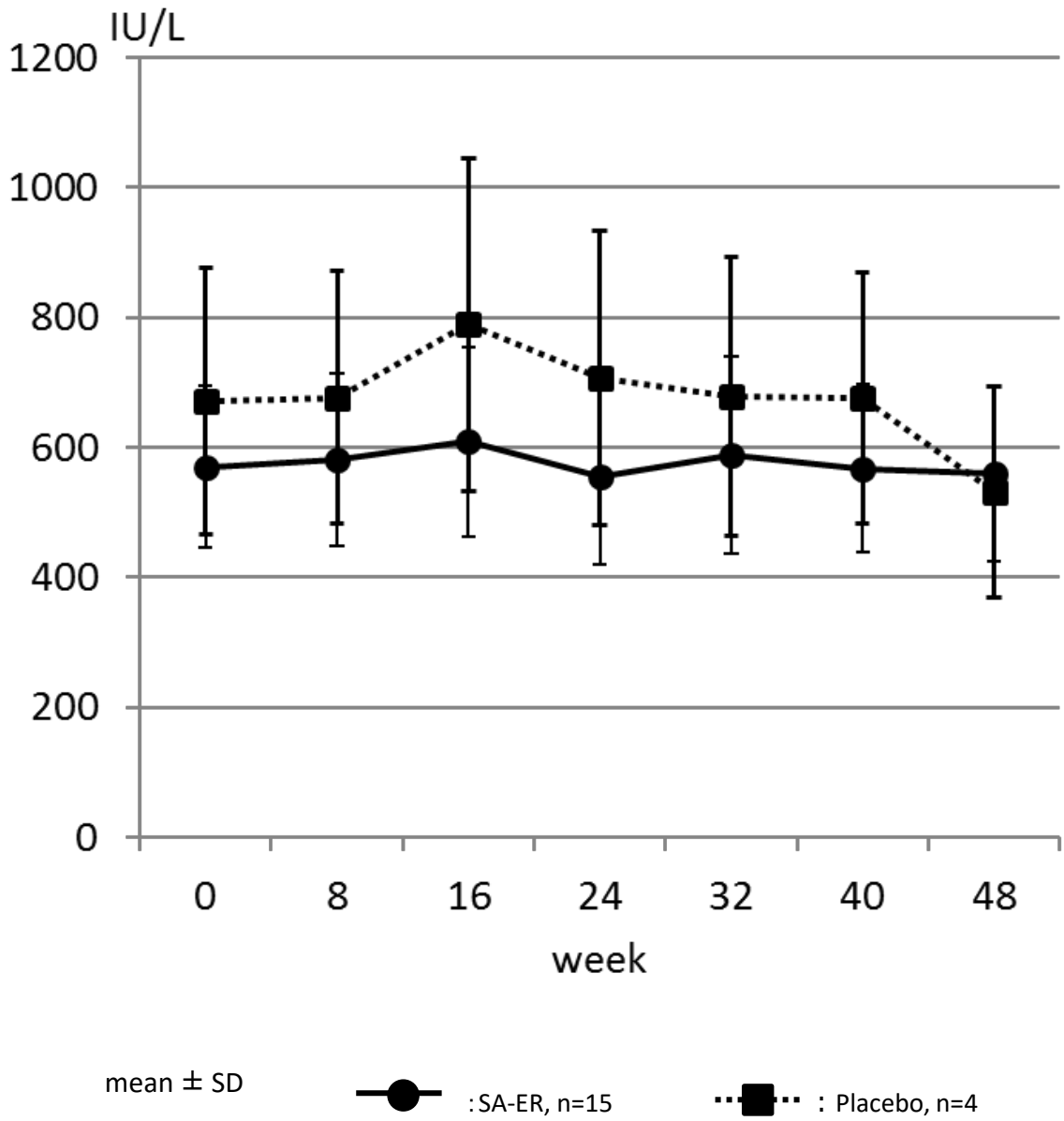
—●— : SA-ER, n=15(sit-to-stand test), n=12 (weighted arm lift test)

···■··· : Placebo, n=4

Supplementary Figure 3. Change in sit-to-stand test (a) and weighted arm lift test (b)



Supplementary Figure 4. Change in INQoL



Supplementary Figure 5. Serum creatine kinase concentration

Supplementary Table 1. Schedule of Events

Assessments and events	Screening ^a	Baseline ^e	Treatment Period ^b (weeks)							Follow up ^c
			4(TC)	8	16	24	32	40	48/ET ^a	
Informed consent	x									
Patient's demography										
Age (at time of consent), Sex, Height	x									
Weight	x	x		x	x	x	x	x	x	x
Medical history ^d , Past medical history, Concomitant disease	x									
Pretreatment drug	x									
Concomitant medications, Combination therapy	x	x		x	x	x	x	x	x	x
Clinical evaluation										
Dynamometry	x	x		x	x	x	x	x	x	
6-minute walk test (6MWT)	x	x		x	x	x	x	x	x	
Sit-to-stand test	x	x		x	x	x	x	x	x	
Weighted arm lift test	x	x		x	x	x	x	x	x	
GNE myopathy functional activities scale (GNE-FAS)		x		x	x	x	x	x	x	
Individual neuromuscular quality of life questionnaire (INQoL)		x		x	x	x	x	x	x	
Creatine kinase (CK) ^e	(x)	x		x	x	x	x	x	x	(x)
Clinical global impression scale (CGI) ^f		x				x			x	
Free serum aceneuramic acid ^g		x		x	x	x	x	x	x	
Free, total and bound urine aceneuramic acid ^g	x	x			x		x		x	
Urine ManNAc ^h	x	x			x		x		x	
Interval history ⁱ		x		x	x	x	x	x	x	x
Physical examination ⁱ	x	x ^j		x	x	x ^j	x	x	x ^j	x
Vital sign	x	x		x	x	x	x	x	x	x
12-lead ECG	x	x		x	x	x	x	x	x	x
Clinical laboratory test										
Hematology, Blood biochemistry, Urinalysis	x	x		x	x	x	x	x	x	x
Pregnancy test (Presence or absence of pregnancy for partners in a male subject)	x	X			x		x		x	x
Suicidal ideation and behavior ^k	x	X		x	x	x	x	x	x	x
Adverse events	x	X	x ^b	x	x	x	x	x	x	x
Treatment dispensed		X		x	x	x	x	x		
Treatment compliance ^l				x	x	x	x	x	x	

* Refer to test procedure for recommended timing and order of assessments to be administered at each study visit

a Conducted after informed consent. Subject candidate will be screened approximately 7 days (up to 28 days) before baseline visit. Prescribe the study drug only after all the study measurements have been performed. For subjects who discontinue prior to completing the study, every reasonable effort should be made to perform the Early Termination (ET) procedures within four weeks of discontinuation.

b Visits occur every 8 weeks ± 5 days. For abbreviated safety assessment, subjects will be contacted by telephone call (TC) at 4 weeks after starting administration. Additional unscheduled telephone calls may be performed from time to time to confirm patient tracking. Unscheduled visits for safety confirmation and medication are allowed.

c The visits for the safety tracking of the subject is conducted 4 weeks (± 5 days) after the final administration of the investigational drug. (i.e. at 52 weeks)

d Medical history will be a detailed GNE myopathy treatment history.

e It is also a safety evaluation item (clinical laboratory test). It works only as a safety assessment item at screening or at the end of treatment.

f In clinical global impression the CGI-severity scale is evaluated before administration (0 week). In addition, three target areas for disease improvement are specified. The CGI-improvement scale will be assessed at the subsequent visit for the three target areas specified before administration.

g Serum and blank urine are collected and the trough value of the aceneuramic acid concentrations are measured. Record urine volume.

h Specimens of blank urine in the early morning are used for evaluation of ManNAc. Record the amount of urine collected.

i Interval history will include any signs, symptoms, or events (i.e. falls) experienced by the subject since the prior study visit that are not related to study procedure(s) performed at prior study visits or study drug. Interval history may include exacerbation or improvement in existing medical conditions (including the clinical manifestations of GNEM) that might interfere with study participation, safety, and/or positively or negatively impact performance of functional assessments.

j The physical examinations at Baseline and Weeks 24 and 48 will be complete examination, including a neurological examination. All others will be brief physical examinations.

k C-SSRS at screening and before administration is a slightly different questionnaire style from all subsequent visits.

l The subject is instructed to return unused study drugs at every visit.

Supplementary Table 2. Demographic and Baseline Characteristics (Full analysis set)

Characteristic		SA-ER 6 g/day n=15	Placebo n=4	Total n=19	t-test or χ^2 -test
Age (years)	mean±SD	41±7	37±1	40±6	0.238
	median(min,max)	42(26, 48)	37(35, 38)	42(26, 48)	
Sex	male	5(33.3)	2(50.0)	7(36.8)	0.539
	female	10(66.7)	2(50.0)	12(63.2)	
Height(cm)	mean±SD	164.5±8.2	169.7±11.3	165.6±8.8	0.307
	median(min,max)	164.2(153.4, 177.6)	168.7(158.7, 182.8)	164.2(153.4, 182.8)	
Weight(kg)	mean±SD	60.6±15.8	63.0±10.5	61.1±14.6	0.781
	median(min,max)	60.0(39.7, 94.1)	65.1(48.5, 73.4)	63.8(39.7, 94.1)	
6-minutes walking test	mean±SD	323.4±104.1	281.0±65.0	314.5±97.2	0.454
	median(min,max)	324.0(140.0, 507.4)	273.5(210.0, 367.0)	296.3(140.0, 507.4)	
	<200 m	1(6.7)	0(0.0)	1(5.3)	
	≥200 m	14(93.3)	4(100.0)	18(94.7)	0.596
6-minutes walking test (% predicted)	mean±SD	46.8±15.6	38.7±7.1	45.1±14.5	0.339
	median(min,max)	45.3(19.3, 70.0)	38.1(30.7, 48.0)	41.0(19.3, 70.0)	
Sit-to-stand test	mean±SD	11.0±6.6	12.8±3.9	11.4±6.1	0.623
	median(min,max)	12(0, 19)	12(9, 18)	12(0, 19)	
Weighted arm lift test	mean±SD	24.8±9.9*	23.8±18.5	24.5±11.8	0.890
	median(min,max)	23.5(10, 46.5)	25(0, 45)	24.8(0.0, 46.5)	
Age at symptom onset(years)	mean±SD	30±7	27±1	29±6	0.450
	median(min,max)	30(13, 40)	27(26, 27)	27(13, 40)	
Disease duration(years)	mean±SD	11±5	10±1	11±5	0.618
	median(min,max)	10(5, 22)	11(8, 11)	10(5, 22)	
Serum free aceneuramic acid (µg/mL)	mean±SD	0.150±0.058	0.149±0.029	0.150±0.052	0.972
	median(min,max)	0.140(0.106, 0.335)	0.152(0.118, 0.175)	0.140(0.106, 0.335)	
HHD upper extremity muscle strength(kg)					
Gross grip	mean±SD	12.6±10.2	21.0±14.0	14.4±11.2	0.191
	median(min,max)	11.0(0.0, 31.0)	20.0(5.0, 39.0)	13.0(0.0, 39.0)	
Elbow flexors	mean±SD	7.0±4.8	9.2±4.2	7.4±4.7	0.408
	median(min,max)	6.8(0.0, 19.8)	9.2(4.4, 14.2)	7.5(0.0, 19.8)	
Elbow extensors	mean±SD	4.2±2.8	6.0±3.0	4.5±2.9	0.282
	median(min,max)	3.7(0.0, 8.6)	7.4(1.4, 7.7)	4.3(0.0, 8.6)	
Shoulder abductors	mean±SD	7.8±4.2	9.9±5.7	8.2±4.4	0.412
	median(min,max)	6.6(3.7, 20.9)	10.2(2.7, 16.5)	6.7(2.7, 20.9)	
UEC score	mean±SD	31.5±14.6	46.0±22.7	34.6±17.0	0.131
	median(min,max)	29.6(7.4, 55.9)	53.7(13.5, 63.4)	33.8(7.4, 63.4)	
HHD lower extremity muscle strength(kg)					
Hip flexors	mean±SD	6.3±6.8	6.3±5.4	6.3±6.4	0.993
	median(min,max)	4.5(0.0, 27.9)	6.2(0.0, 13.0)	4.9(0.0, 27.9)	
Hip extensors	mean±SD	9.4±3.9**	12.1±4.3	10.0±4.0	0.252
	median(min,max)	8.9(3.0, 18.4)	10.2(9.6, 18.6)	9.3(3.0, 18.6)	
Hip abductors	mean±SD	7.7±3.5	6.4±3.4	7.4±3.4	0.500
	median(min,max)	7.2(2.8, 17.5)	5.5(3.3, 11.1)	6.8(2.8, 17.5)	
Hip adductors	mean±SD	4.8±5.0	3.1±3.2	4.5±4.6	0.532
	median(min,max)	3.1(0.0, 17.6)	1.9(1.0, 7.9)	2.8(0.0, 17.6)	
Knee flexors	mean±SD	5.2±5.5	3.7±2.4	4.9±5.0	0.603
	median(min,max)	3.7(0.7, 22.5)	3.0(1.8, 7.0)	3.7(0.7, 22.5)	
LEC score	mean±SD	29.1±13.3**	31.6±18.1	29.6±13.9	0.759
	median(min,max)	28.3(7.3, 59.8)	26.3(16.4, 57.4)	28.3(7.3, 59.8)	
Knee extensors	mean±SD	16.3±4.7**	17.7±9.3	16.6±5.7	0.682
	median(min,max)	15.9(10.5, 26.3)	14.9(10.3, 30.7)	15.9(10.3, 30.7)	
HHD upper extremity muscle strength(% predicted)					
Gross grip	mean±SD	36.8±29.1	51.8±27.3	40.0±28.7	0.367
	median(min,max)	37.9(0.0, 105.0)	54.1(17.2, 81.9)	41.2(0.0, 105.0)	
Elbow flexors	mean±SD	34.9±21.7	39.6±17.4	35.9±20.5	0.875
	median(min,max)	38.3(0.0, 69.9)	37.1(24.4, 59.9)	38.3(0.0, 69.9)	
Elbow extensors	mean±SD	28.7±19.2	35.0±19.1	30.0±18.9	0.696
	median(min,max)	27.8(0.0, 64.8)	35.1(11.5, 58.3)	33.1(0.0, 64.8)	
Shoulder abductors	mean±SD	50.7±21.4	52.7±25.4	51.1±21.6	0.568
	median(min,max)	49.5(17.6, 92.9)	56.3(21.9, 76.3)	49.5(17.6, 92.9)	
UEC score	mean±SD	37.8±17.5	44.8±19.0	39.3±17.5	0.492
	median(min,max)	36.5(8.9, 75.1)	48.1(18.8, 64.1)	38.6(8.9, 75.1)	
HHD lower extremity muscle strength(% predicted)					
Hip flexors	mean±SD	15.6±13.4	12.5±9.5	15.0±12.5	0.671
	median(min,max)	12.7(0.0, 51.7)	13.4(0.0, 23.2)	12.8(0.0, 51.7)	
Hip extensors	mean±SD	31.7±16.4**	33.5±8.4	32.1±14.8	0.844
	median(min,max)	30.8(6.8, 68.6)	35.2(21.8, 41.7)	33.0(6.8, 68.6)	
Hip abductors	mean±SD	35.4±14.0	24.7±8.2	33.1±13.6	0.328
	median(min,max)	35.5(9.4, 60.3)	22.0(18.1, 36.6)	35.5(9.4, 60.3)	
Hip adductors	mean±SD	20.9±18.8	11.0±9.2	18.8±17.5	0.167
	median(min,max)	15.7(0.0, 66.3)	7.0(5.1, 24.7)	14.1(0.0, 66.3)	
Knee flexors	mean±SD	25.9±23.9	15.5±7.4	23.7±21.7	0.411
	median(min,max)	15.0(2.8, 87.6)	13.1(9.8, 26.1)	15.0(2.8, 87.6)	
LEC score	mean±SD	23.7±12.9**	19.4±7.5	22.7±11.8	0.544
	median(min,max)	23.4(4.3, 56.5)	16.6(14.0, 30.5)	22.4(4.3, 56.5)	
Knee extensors	mean±SD	45.2±13.7**	41.8±16.9	44.5±14.0	0.675
	median(min,max)	45.2(20.3, 65.8)	42.7(23.1, 58.5)	45.2(20.3, 65.8)	

Note)*:n=12, **:n=14

Supplementary Table 3. Tertiary endpoints

	SA-ER			Placebo		
	mean ± SD (n)	95% confidence interval of mean	median(min,max)	mean ± SD (n)	95% confidence interval of mean	median(min,max)
UEC score (% predicted)	0.2 ± 5.4(15)	(-2.8, 3.1)	-0.4 (-8.6, 10.5)	-5.4 ± 4.0(4)	(-11.8, 1.0)	-5.1(-9.8, -1.5)
LEC score (% predicted)	1.3 ± 7.6(14)	(-3.1, 5.7)	2.8(-13.4, 12.1)	-2.2 ± 2.6(4)	(-6.3, 1.9)	-1.2(-6.1,-0.5)
Gross grip	-0.4 ± 1.4(15)	(-1.2, 0.4)	-1.0(-2.0, 2.0)	-2.0 ± 2.3(4)	(-5.7, 1.7)	-2.0(-4.0, 0.0)
Elbow flexors	-0.2 ± 1.3(15)	(-0.9, 0.6)	-0.4(-2.0, 2.8)	-1.0 ± 0.9(4)	(-2.4, 0.5)	-0.9(-2.1, 0.1)
Elbow extensors	-0.1 ± 0.9(15)	(-0.6, 0.4)	-0.3(-1.3, 2.8)	-0.3 ± 1.5(4)	(-2.8, 2.1)	-0.8(-1.6, 1.8)
Shoulder abductors	0.6 ± 1.3(15)	(-0.2, 1.3)	0.9(-2.0, 2.8)	-1.8 ± 1.0(4)	(-3.4, -0.2)	-1.9(-2.9, -0.6)
Hip flexors	0.9 ± 4.2(15)	(-1.4, 3.2)	0.0(-5.4, 13.5)	-1.0 ± 1.1(4)	(-2.8, 0.8)	-0.9(-2.4, 0.0)
Hip extensors	0.7 ± 3.1(14)	(-1.1, 2.5)	0.4(-5.1, 6.6)	-1.1 ± 3.0(4)	(-5.9, 3.8)	-1.0(-4.4, 2.3)
Hip abductors	1.3 ± 3.7(15)	(-0.7, 3.4)	0.4(-4.5, 8.5)	0.0 ± 0.8(4)	(-1.2, 1.3)	-0.2(-0.6, 1.1)
Hip adductors	0.6 ± 2.2(15)	(-0.6, 1.9)	0.3(-2.3, 7.2)	-0.9 ± 1.6(4)	(-3.5, 1.8)	-0.4(-3.2, 0.6)
Knee flexors	0.5 ± 2.2(15)	(-0.7, 1.8)	0.4(-2.9, 5.9)	-0.9 ± 1.4(4)	(-3.0, 1.3)	-0.7(-2.8, 0.5)
Gross grip (% predicted)	-0.9 ± 4.6(15)	(-3.5, 1.6)	-2.1(-7.0, 7.0)	-4.2 ± 4.8(4)	(-11.9, 3.5)	-4.2(-8.4, 0.0)
Elbow flexors (% predicted)	-1.2 ± 7.4(15)	(-5.2, 2.9)	-1.3(-11.1, 15.7)	-4.8 ± 4.9(4)	(-12.6, 3.0)	-4.0(-11.4, 0.4)
Elbow extensors (% predicted)	-0.7 ± 6.7(15)	(-4.4, 3.0)	-2.2(-9.6, 20.1)	-2.7 ± 8.7	(-16.5, 11.1)	-3.7(-11.7, 8.4)
Shoulder abductors (% predicted)	3.5 ± 9.1(15)	(-1.5, 8.6)	5.9(-14.3, 19.4)	-9.9 ± 5.2(4)	(-18.2, -1.6)	-9.3(-16.2, -4.9)
Hip flexors (% predicted)	1.8 ± 9.1(15)	(-3.3, 6.8)	0.0(-15.4, 25.0)	-2.2 ± 2.4(4)	(-6.0, 1.5)	-2.3(-4.4, 0.0)
Hip extensors (% predicted)	1.5 ± 9.8(14)	(-4.1, 7.1)	1.6(-17.9, 21.3)	-2.9 ± 7.7(4)	(-15.1, 9.3)	-3.5(-9.9, 5.1)
Hip abductors (% predicted)	4.8 ± 16.3(15)	(-4.2, 13.8)	2.6(-21.3, 31.9)	0.2 ± 3.5(4)	(-5.4, 5.8)	-0.9(-2.5, 5.1)
Hip adductors (% predicted)	2.3 ± 7.9(15)	(-2.1, 6.7)	1.3(-7.1, 22.7)	-2.6 ± 5.5(4)	(-11.4, 6.1)	-1.8(-10.1, 3.1)
Knee flexors (% predicted)	1.5 ± 10.1(15)	(-4.1, 7.1)	1.8(-16.4, 23.3)	-3.5 ± 5.4(4)	(-12.0, 5.1)	-3.2(-10.3, 2.7)
GNEM-FAS self-care domain	0.3 ± 1.8(15)	(-0.7, 1.3)	0.0 (-2, 4)	-2.0 ± 2.9(4)	(-6.7, 2.7)	-1.5(-6, 1)
GNEM-FAS total score	0.5 ± 5.0(15)	(-2.2, 3.3)	0.0(-11, 8)	-2.3 ± 6.2(4)	(-12.1, 7.6)	-0.5(-11, 3)
INQoL*3	7.6 ± 17.6(15)	(-2.1, 17.4)	4.4(-24.4, 49.4)	7.8 ± 16.7(4)	(-18.8, 34.3)	6.4(-11.1, 29.4)
Serum creatine kinase	-11.1 ± 213.3(15)	(-129.2, 107.0)	-9(-516, 437)	-139.0 ± 232.7(4)	(-509.3, 231.3)	-104.0(-450, 102)
Serum free aceneuramic acid	0.393 ± 0.423(15)	(0.158, 0.627)	0.309(0.019, 1.816)	-0.002 ± 0.030(4)	(-0.049, 0.045)	0.010(-0.045, 0.019)
Urinary free aceneuramic acid*4	80.2 ± 184.9(15)	(-22.2, 182.6)	52.3(-243.7, 550.2)	26.8 ± 34.1(4)	(-27.5, 81.0)	13.4(2.9, 77.3)
Urinary total aceneuramic acid*4	59.3 ± 358.3(15)	(-139.1, 257.7)	89.1(-834.8, 854.0)	144.7 ± 171.5(4)	(-128.2, 417.6)	75.7(31.9, 395.6)
Urinary combined aceneuramic acid*4	-20.9 ± 193.4(15)	(-128.0, 86.2)	22.5(-591.2, 303.9)	117.9 ± 137.8(4)	(-101.4, 337.3)	64.1(25.3, 318.3)

*1)Use baseline data as covariate. Also treatment group, sex and 6MWT as explanatory variables.

*2)Use baseline data as covariate. Also treatment group, time point, sex and 6MWT as fixed effects.

*3)Individualized Neuromuscular Quality of Life Questionnaire

*4)value after creatinine correction

Supplementary Table 4. Number of cases and incidence of adverse events

	SA-ER n=16			Placebo n=4		
	no. of events	no. of subjects	%	no. of events	no. of subjects	%
Total	67	14	87.5	10	3	75
Infections and infestations	21	12	75	4	3	75
Angular cheilitis	2	2	12.5	0	0	0
Dermatophytosis of nail	0	0	0	1	1	25
Gastroenteritis	1	1	6.3	1	1	25
Gastroenteritis viral	2	2	12.5	0	0	0
Gingivitis	1	1	6.3	0	0	0
Hordeolum	1	1	6.3	0	0	0
Influenza	2	2	12.5	0	0	0
Otitis externa	3	2	12.5	0	0	0
Sinusitis	1	1	6.3	1	1	25
Viral upper respiratory tract infection	8	7	43.8	1	1	25
Immune system disorder	1	1	6.3	0	0	0
Hypersensitivity	1	1	6.3	0	0	0
Mental disorder	1	1	6.3	0	0	0
Insomnia	1	1	6.3	0	0	0
Nervous system disorder	3	3	18.8	1	1	25
Headache	3	3	18.8	0	0	0
Hypoesthesia	0	0	0	1	1	25
Gastrointestinal disorder	8	5	31.3	2	2	50
Abdominal discomfort	1	1	6.3	0	0	0
Abdominal pain upper	1	1	6.3	0	0	0
Chronic gastritis	1	1	6.3	0	0	0
Constipation	1	1	6.3	0	0	0
Dental caries	1	1	6.3	0	0	0
Diarrhoea	1	1	6.3	0	0	0
Gastritis	0	0	0	1	1	25
Nausea	2	1	6.3	0	0	0
Stomatitis	0	0	0	1	1	25
Hepatobiliary disorders	2	2	12.5	0	0	0
Cholelithiasis	1	1	6.3	0	0	0
Hepatic function disorder	1	1	6.3	0	0	0
Skin and subcutaneous tissue disorders	3	2	12.5	2	1	25
Eczema	1	1	6.3	0	0	0
Miliaria	0	0	0	1	1	25
Rash	2	1	6.3	0	0	0
Seborrhoeic dermatitis	0	0	0	1	1	25
Musculoskeletal and connective tissue disorders	5	5	31.3	0	0	0
Arthralgia	1	1	6.3	0	0	0
Back pain	1	1	6.3	0	0	0
Pain in extremity	2	2	12.5	0	0	0
Tenosynovitis	1	1	6.3	0	0	0
Renal and urinary disorders	1	1	6.3	0	0	0
Calculus urinary	1	1	6.3	0	0	0
Pregnancy, puerperium and perinatal conditions	1	1	6.3	0	0	0
Foetal death	1	1	6.3	0	0	0
Reproductive system and breast disorders	1	1	6.3	0	0	0
Menopausal symptoms	1	1	6.3	0	0	0
Injury, poisoning and procedural complications	20	8	50	1	1	25
Facial bones fracture	1	1	6.3	0	0	0
Fall	7	4	25	1	1	25
Ligament sprain	1	1	6.3	0	0	0
Subcutaneous haematoma	1	1	6.3	0	0	0
Excoriation	2	2	12.5	0	0	0
Contusion	7	4	25	0	0	0
Tooth fracture	1	1	6.3	0	0	0