

Appendix 1-1. ALT, AST, γ -GT, AST/ALT ratio (4wks and 4wks-Scr / PPS)

	Reference range	Unit	4wks			4wks-Scr			
			Mean	SD	<i>P</i> value	Mean	SD	<i>P</i> value	
ALT	≤ 30	U/L	Active group (<i>n</i> = 31)	34.3	11.9	0.61	-3.7	13.0	0.60
			Placebo group (<i>n</i> = 31)	37.3	16.1		-1.8	13.5	
AST	10-40	U/L	Active group (<i>n</i> = 31)	29.0	12.0	0.62	-1.2	12.0	0.59
			Placebo group (<i>n</i> = 31)	29.8	10.9		0.3	8.5	
γ -GT	Male: ≤ 80	U/L	Active group (<i>n</i> = 31)	83.5	78.3	0.79	3.7	33.2	0.94
	Female: ≤ 30		Placebo group (<i>n</i> = 31)	68.4	58.4		3.7	27.5	
AST/ALT ratio	-	-	Active group (<i>n</i> = 31)	0.9	0.3	0.87	0.1	0.3	0.92
			Placebo group (<i>n</i> = 31)	0.8	0.2		0.1	0.1	

The data are presented as the mean and standard deviation (SD). The baseline (Scr) values are evaluated using Student's *t*-test, the measured values are evaluated using Post-hoc comparisons with linear mixed model, with the baseline values utilized as covariates and time, group, group-time interaction, and subject as factors, and the changes are evaluated using Post-hoc comparisons with linear mixed model, with time, group, group-time interaction, and subject as factors.

*: *P* < 0.05 vs. the placebo group.

Appendix 1-2. ALT, AST, γ -GT, AST/ALT ratio (4wks and 4wks-Scr / PPS / Men)

	Reference range	Unit	4wks			4wks-Scr			
			Mean	SD	<i>P</i> value	Mean	SD	<i>P</i> value	
ALT	≤30	U/L	Active group (<i>n</i> = 25)	33.7	11.9	0.37	-4.7	12.3	0.38
			Placebo group (<i>n</i> = 26)	37.0	15.2		-1.2	12.5	
AST	10-40	U/L	Active group (<i>n</i> = 25)	27.9	10.1	0.41	-1.5	8.7	0.41
			Placebo group (<i>n</i> = 26)	29.3	10.0		0.5	8.3	
γ -GT	≤80	U/L	Active group (<i>n</i> = 25)	76.3	70.7	0.37	-0.6	31.8	0.41
			Placebo group (<i>n</i> = 26)	73.2	62.2		6.0	27.7	
AST/ALT ratio	-	-	Active group (<i>n</i> = 25)	0.9	0.3	0.69	0.1	0.3	0.68
			Placebo group (<i>n</i> = 26)	0.8	0.2		0.1	0.1	

The data are presented as the mean and standard deviation (SD). The baseline (Scr) values are evaluated using Student's *t*-test, the measured values are evaluated using Post-hoc comparisons with linear mixed model, with the baseline values utilized as covariates and time, group, group-time interaction, and subject as factors, and the changes are evaluated using Post-hoc comparisons with linear mixed model, with time, group, group-time interaction, and subject as factors.

Appendix 1-3. ALT, AST, γ -GT, AST/ALT ratio (4wks and 4wks-Scr / PPS / Women)

	Reference range	Unit	4wks			4wks-Scr			
			Mean	SD	<i>P</i> value	Mean	SD	<i>P</i> value	
ALT	≤ 30	U/L	Active group (<i>n</i> = 6)	36.8	12.7	0.93	0.3	16.3	0.62
			Placebo group (<i>n</i> = 5)	39.0	22.3		-4.4	19.1	
AST	10-40	U/L	Active group (<i>n</i> = 6)	33.7	18.4	0.89	0.3	22.3	0.91
			Placebo group (<i>n</i> = 5)	32.4	15.8		-0.8	10.9	
γ -GT	≤ 30	U/L	Active group (<i>n</i> = 6)	113.2	107.1	0.18	21.7	35.5	0.09
			Placebo group (<i>n</i> = 5)	44.4	25.5		-7.4	26.4	
AST/ALT ratio	-	-	Active group (<i>n</i> = 6)	0.9	0.3	0.63	0.0	0.2	0.51
			Placebo group (<i>n</i> = 5)	0.9	0.1		0.1	0.2	

The data are presented as the mean and standard deviation (SD). The baseline (Scr) values are evaluated using Student's *t*-test, the measured values are evaluated using Post-hoc comparisons with linear mixed model, with the baseline values utilized as covariates and time, group, group-time interaction, and subject as factors, and the changes are evaluated using Post-hoc comparisons with linear mixed model, with time, group, group-time interaction, and subject as factors.

Appendix 2-1. OSA-MA (4wks and 4wks-Scr / FAS)

	Unit		4wks			4wks-Scr		
			Mean	SD	<i>P</i> value	Mean	SD	<i>P</i> value
Sleepiness on rising	point	Active group (<i>n</i> = 33)	20.6	5.3	0.89	-0.4	6.0	0.65
		Placebo group (<i>n</i> = 33)	20.7	5.0		-1.1	5.6	
Initiation and maintenance of sleep	point	Active group (<i>n</i> = 33)	20.2	3.7	0.76	0.2	4.4	0.97
		Placebo group (<i>n</i> = 33)	20.7	5.1		0.1	5.8	
Frequent dreaming	point	Active group (<i>n</i> = 33)	24.1	5.4	0.42	-0.4	4.7	0.19
		Placebo group (<i>n</i> = 33)	24.3	4.8		1.4	5.3	
Feeling refreshing	point	Active group (<i>n</i> = 33)	20.6	5.3	0.70	-0.8	7.5	0.52
		Placebo group (<i>n</i> = 33)	20.3	5.9		-1.8	6.5	
Sleep length	point	Active group (<i>n</i> = 33)	22.3	5.9	0.10	-0.9	5.2	0.08
		Placebo group (<i>n</i> = 33)	20.6	6.5		-3.3	6.2	
Question 1 (remaining fatigue)	point	Active group (<i>n</i> = 33)	20.4	5.4	0.54	-0.8	8.5	0.73
		Placebo group (<i>n</i> = 33)	19.5	6.1		-1.5	7.8	
Question 2 (concentration ability)	point	Active group (<i>n</i> = 33)	20.3	6.2	0.71	-1.4	7.6	0.96
		Placebo group (<i>n</i> = 33)	21.1	6.0		-1.3	7.8	
Question 3 (deepness of sleep)	point	Active group (<i>n</i> = 33)	17.8	5.4	0.68	0.1	6.5	0.59
		Placebo group (<i>n</i> = 33)	19.2	6.6		-0.9	7.2	
Question 4 (relaxing)	point	Active group (<i>n</i> = 33)	20.8	6.3	0.68	0.4	8.3	0.93
		Placebo group (<i>n</i> = 33)	20.2	5.8		0.6	8.6	
Question 5 (dullness)	point	Active group (<i>n</i> = 33)	18.7	5.8	0.96	-1.5	7.9	0.83
		Placebo group (<i>n</i> = 33)	18.9	6.2		-1.8	6.4	

Question 6 (appetite)	point	Active group (<i>n</i> = 33)	23.1	8.6	0.31	-3.4	6.8	0.28
		Placebo group (<i>n</i> = 33)	21.9	7.7		-5.2	7.4	
Question 7 (dozing off)	point	Active group (<i>n</i> = 33)	22.2	7.0	0.38	-0.2	8.7	0.22
		Placebo group (<i>n</i> = 33)	23.0	5.5		2.1	7.7	
Question 8 (clearness of thought)	point	Active group (<i>n</i> = 33)	20.4	6.4	0.39	0.2	7.6	0.22
		Placebo group (<i>n</i> = 33)	19.6	5.9		-2.1	7.4	
Question 9 (nightmares)	point	Active group (<i>n</i> = 33)	26.6	4.4	0.90	0.6	3.4	0.53
		Placebo group (<i>n</i> = 33)	26.2	4.0		1.4	5.4	
Question 10 (quality of sleep)	point	Active group (<i>n</i> = 33)	19.6	6.1	0.40	2.0	6.7	0.30
		Placebo group (<i>n</i> = 33)	18.9	7.5		0.1	8.1	
Question 11 (feelings)	point	Active group (<i>n</i> = 33)	22.8	6.7	0.59	-0.1	8.1	0.26
		Placebo group (<i>n</i> = 33)	22.5	6.5		-2.2	7.5	
Question 12 (dreaming)	point	Active group (<i>n</i> = 33)	21.6	8.1	0.30	-1.5	7.9	0.15
		Placebo group (<i>n</i> = 33)	22.4	7.0		1.4	6.9	
Question 13 (waking at night)	point	Active group (<i>n</i> = 33)	21.0	5.9	0.78	-0.4	5.7	0.83
		Placebo group (<i>n</i> = 33)	21.9	5.9		-0.7	8.0	
Question 14 (answering ability)	point	Active group (<i>n</i> = 33)	20.7	6.6	0.94	-0.8	6.7	0.64
		Placebo group (<i>n</i> = 33)	22.0	6.2		-1.5	5.5	
Question 15 (sleeping time)	point	Active group (<i>n</i> = 33)	21.5	5.9	0.07	1.7	6.1	0.07
		Placebo group (<i>n</i> = 33)	19.3	7.7		-1.3	7.5	
Question 16 (deepness of sleep)	point	Active group (<i>n</i> = 33)	20.1	6.2	0.70	-0.6	8.0	0.74
		Placebo group (<i>n</i> = 33)	20.7	6.9		0.0	7.0	

The data are presented as the mean and standard deviation (SD). The baseline (Scr) values are evaluated using Student's *t*-test, the measured values are evaluated using Post-hoc comparisons with linear

mixed model, with the baseline values utilized as covariates and time, group, group–time interaction, and subject as factors, and the changes are evaluated using Post-hoc comparisons with linear mixed model, with time, group, group–time interaction, and subject as factors.

*: $P < 0.05$ vs. the placebo group.

Appendix 2-2. OSA-MA (4wks and 4wks-Scr / subgroup analysis of subjects aged 45 years and older in FAS)

Unit	Scr			4wks			8wks			4wks-Scr			8wks-Scr			
	Mean	SD	<i>P</i> value	Mean	SD	<i>P</i> value	Mean	SD	<i>P</i> value	Mean	SD	<i>P</i> value	Mean	SD	<i>P</i> value	
Sleepiness on rising	Active group (<i>n</i> = 18)	20.1	4.5	0.15	19.8	4.6	0.91	20.6	5.2	0.55	-0.3	3.5	0.44	0.5	4.9	0.17
	Placebo group (<i>n</i> = 18)	22.7	6.1		21.0	4.2		20.7	5.7		-1.8	5.4		-2.0	7.6	
Initiation and maintenance of sleep	Active group (<i>n</i> = 18)	19.7	5.1	0.29	20.3	3.6	0.30	21.0	5.2	0.15	0.7	4.9	0.14	1.3	4.1	0.07
	Placebo group (<i>n</i> = 18)	21.7	6.0		19.7	5.4		19.7	4.6		-2.0	6.0		-2.0	5.8	
Frequent dreaming	Active group (<i>n</i> = 18)	26.9	4.0	0.07	25.2	4.9	0.73	24.5	5.5	0.47	-1.7	3.7	0.19	-2.3	5.4	0.68
	Placebo group (<i>n</i> = 18)	23.6	6.2		24.5	4.8		22.1	5.3		0.8	6.1		-1.6	7.0	
Feeling refreshing	Active group (<i>n</i> = 18)	21.0	4.5	0.34	20.7	4.7	0.31	21.9	6.0	0.09	-0.4	3.5	0.17	0.9	5.3	0.047*
	Placebo group (<i>n</i> = 18)	22.6	5.4		19.6	5.5		19.6	5.6		-3.0	6.2		-3.0	7.2	
Sleep length	Active group (<i>n</i> = 18)	22.3	4.5	0.36	21.4	5.6	0.45	22.7	4.9	0.77	-0.8	5.1	0.28	0.4	3.7	0.50
	Placebo group (<i>n</i> = 18)	23.9	6.0		21.1	6.9		23.1	5.2		-2.9	6.7		-0.9	6.2	

question 1 (remaining fatigue)	point	Active group (<i>n</i> = 18)	20.9	5.3		20.4	4.2		21.3	5.3		-0.6	5.1		0.4	6.3	
		Placebo group (<i>n</i> = 18)	21.4	6.9	0.83	18.7	6.1	0.33	18.5	6.5	0.12	-2.7	8.0	0.38	-2.9	9.0	0.18
question 2 (concentration ability)	point	Active group (<i>n</i> = 18)	20.4	5.0		19.1	5.7		21.4	5.8		-1.4	5.0		0.9	7.1	
		Placebo group (<i>n</i> = 18)	23.9	8.5	0.14	20.8	5.4	0.64	21.8	6.1	0.78	-3.1	7.9	0.49	-2.2	9.4	0.22
question 3 (deepness of sleep)	point	Active group (<i>n</i> = 18)	16.9	5.8		16.9	5.2		19.3	6.8		-0.1	5.3		2.4	6.5	
		Placebo group (<i>n</i> = 18)	20.9	7.5	0.09	18.0	6.8	0.85	18.8	5.5	0.30	-2.9	7.3	0.23	-2.1	8.5	0.06
question 4 (relaxing)	point	Active group (<i>n</i> = 18)	20.6	4.8		20.2	4.9		21.8	4.7		-0.4	4.4		1.2	5.8	
		Placebo group (<i>n</i> = 18)	19.2	8.5	0.54	19.3	5.7	0.71	19.3	6.0	0.20	0.2	9.7	0.83	0.1	10.1	0.69
question 5 (dullness)	point	Active group (<i>n</i> = 18)	19.2	4.7		18.6	5.8		20.8	6.9		-0.6	4.5		1.6	7.0	
		Placebo group (<i>n</i> = 18)	21.3	5.6	0.22	18.3	5.7	0.53	18.0	5.6	0.05	-3.0	6.0	0.25	-3.3	7.1	0.021*
question 6 (appetite)	point	Active group (<i>n</i> = 18)	25.9	8.0		22.2	8.2		23.7	8.9		-3.7	6.9		-2.2	5.3	
		Placebo group (<i>n</i> = 18)	28.7	7.5	0.28	23.3	7.2	0.69	25.6	7.7	0.98	-5.4	7.8	0.42	-3.1	6.2	0.69

question 7 (dozing off)	point	Active group (<i>n</i> = 18)	20.7	6.3		22.5	6.0		22.6	5.6		1.8	8.3		1.8	5.4
		Placebo group (<i>n</i> = 18)	23.2	7.3	0.29				0.47			0.31			0.22	
question 8 (clearness of thought)	point	Active group (<i>n</i> = 18)	19.7	6.5		19.8	6.2		20.1	6.6		0.2	6.8		0.4	6.3
		Placebo group (<i>n</i> = 18)	23.2	6.5	0.11				0.62			0.51			0.18	
question 9 (nightmares)	point	Active group (<i>n</i> = 18)	27.5	4.6		27.4	4.1		26.2	4.3		-0.1	2.3		-1.3	5.8
		Placebo group (<i>n</i> = 18)	25.7	6.0	0.31				0.64			0.32			0.78	
question 10 (quality of sleep)	point	Active group (<i>n</i> = 18)	17.8	7.2		20.2	5.6		19.8	6.1		2.4	7.8		1.9	6.6
		Placebo group (<i>n</i> = 18)	19.8	7.2	0.41				0.21			0.38			0.13	
question 11 (feelings)	point	Active group (<i>n</i> = 18)	23.0	5.3		23.1	6.2		23.6	6.7		0.1	4.5		0.6	5.0
		Placebo group (<i>n</i> = 18)	25.2	5.9	0.24				0.27			0.26			0.13	
question 12 (dreaming)	point	Active group (<i>n</i> = 18)	26.2	5.0		22.9	7.2		22.9	7.3		-3.3	6.5		-3.3	6.9
		Placebo group (<i>n</i> = 18)	21.6	7.7	0.040*				0.39			0.74			0.07	

question 13 (waking at night)	point	Active group (<i>n</i> = 18)	21.8	6.4		21.7	5.4		21.7	6.6		-0.1	5.4		-0.2	6.7
		Placebo group (<i>n</i> = 18)	22.4	6.2	0.79	20.1	6.5	0.33	19.3	5.1	0.19	-2.3	9.0	0.35	-3.1	6.6
question 14 (answering ability)	point	Active group (<i>n</i> = 18)	19.7	6.5		20.1	6.4		19.2	6.3		0.4	5.8		-0.4	5.3
		Placebo group (<i>n</i> = 18)	24.6	5.4	0.018*	23.6	4.5	0.67	21.7	6.9	0.85	-1.0	4.6	0.47	-2.9	6.8
question 15 (sleeping time)	point	Active group (<i>n</i> = 18)	18.7	5.2		20.7	5.9		21.7	4.2		2.0	6.7		3.0	4.2
		Placebo group (<i>n</i> = 18)	19.1	6.9	0.83	18.8	8.5	0.29	20.5	5.8	0.47	-0.3	7.3	0.30	1.4	7.4
question 16 (deepness of sleep)	point	Active group (<i>n</i> = 18)	21.1	6.9		20.4	5.9		21.6	6.2		-0.7	7.7		0.5	6.1
		Placebo group (<i>n</i> = 18)	22.2	7.2	0.66	20.0	7.2	0.67	20.3	8.3	0.40	-2.2	7.6	0.55	-1.8	7.2

The data are presented as the mean and standard deviation (SD). The baseline (Scr) values are evaluated using Student's *t*-test, the measured values are evaluated using Post-hoc comparisons with linear mixed model, with the baseline values utilized as covariates and time, group, group–time interaction, and subject as factors, and the changes are evaluated using Post-hoc comparisons with linear mixed model, with time, group, group–time interaction, and subject as factors.

*: $P < 0.05$ vs. the placebo group.

Appendix 2-4. OSA–MA (subgroup analysis of subjects under 45 years in FAS)

	Unit		Scr			4wks			8wks			4wks–Scr			8wks–Scr		
			Mean	SD	<i>P</i> value	Mean	SD	<i>P</i> value	Mean	SD	<i>P</i> value	Mean	SD	<i>P</i> value	Mean	SD	<i>P</i> value
Sleepiness on rising	point	Active group (<i>n</i> = 15)	22.0	6.9	0.55	21.5	6.1	0.76	20.6	5.2	0.64	−0.6	8.1	0.93	−1.4	7.3	0.96
		Placebo group (<i>n</i> = 15)	20.7	5.0		20.4	6.0		19.2	6.9		−0.3	6.0		−1.5	5.6	
Initiation and maintenance of sleep	point	Active group (<i>n</i> = 15)	20.4	4.8	0.61	19.9	4.0	0.06	21.0	4.4	0.98	−0.4	3.7	0.06	0.6	5.2	0.74
		Placebo group (<i>n</i> = 15)	19.3	5.9		22.0	4.6		20.5	5.0		2.6	4.5		1.1	4.2	
Frequent dreaming	point	Active group (<i>n</i> = 15)	21.8	6.6	0.93	22.9	5.8	0.54	21.5	6.3	0.23	1.1	5.5	0.62	−0.3	7.1	0.31
		Placebo group (<i>n</i> = 15)	22.0	5.2		24.1	4.9		23.7	6.1		2.1	4.4		1.8	4.5	
Refreshing	point	Active group (<i>n</i> = 15)	21.9	6.9	0.88	20.6	6.1	0.79	20.0	3.9	0.81	−1.3	10.6	0.77	−1.9	7.5	0.94
		Placebo group (<i>n</i> = 15)	21.6	5.3		21.1	6.4		19.4	5.5		−0.5	6.7		−2.1	6.0	
Sleep length	point	Active group (<i>n</i> = 15)	24.2	3.7	0.81	23.3	6.1	0.15	24.9	5.9	0.034*	−0.9	5.5	0.18	0.7	5.7	0.044*
		Placebo group (<i>n</i> = 15)	23.8	6.0		20.0	6.1		20.1	7.8		−3.8	5.7		−3.7	6.3	
Question 1 (remaining fatigue)	point	Active group (<i>n</i> = 15)	21.5	7.6	0.68	20.4	6.7	0.96	18.0	6.3	0.78	−1.1	11.5	0.75	−3.5	9.1	0.63
		Placebo group (<i>n</i> = 15)	20.5	5.6		20.5	6.2		18.6	5.7		0.0	7.5		−1.9	7.1	
Question 2 (concentration ability)	point	Active group (<i>n</i> = 15)	23.3	9.1	0.33	21.9	6.6	0.87	22.0	6.2	0.35	−1.5	10.2	0.45	−1.3	8.7	0.91
		Placebo group (<i>n</i> = 15)	20.5	6.3		21.3	6.9		18.9	7.2		0.8	7.4		−1.7	5.3	
Question 3 (deepness of sleep)	point	Active group (<i>n</i> = 15)	18.5	6.9	0.83	18.8	5.6	0.48	18.6	8.1	0.76	0.3	8.0	0.65	0.1	9.2	0.90
		Placebo group (<i>n</i> = 15)	19.1	6.5		20.6	6.4		19.5	5.8		1.5	6.6		0.4	5.9	
Question 4 (relaxing)	point	Active group (<i>n</i> = 15)	20.2	7.6	0.96	21.5	7.9	0.87	20.5	6.5	0.98	1.3	11.4	0.94	0.3	10.4	0.98
		Placebo group (<i>n</i> = 15)	20.1	5.6		21.1	5.9		20.5	5.5		1.1	7.5		0.4	7.3	
Question 5 (dullness)	point	Active group (<i>n</i> = 15)	21.3	6.4	0.59	18.9	6.1	0.72	18.1	5.6	0.79	−2.5	10.7	0.53	−3.3	9.3	0.57
		Placebo group (<i>n</i> = 15)	20.1	6.2		19.6	6.9		18.6	6.3		−0.5	6.8		−1.5	6.8	

Question 6 (appetite)	point	Active group (<i>n</i> = 15)	27.1	6.6	0.47	24.1	9.3	0.35	26.0	8.0	0.09	-3.1	7.0	0.48	-1.1	6.8	0.14
		Placebo group (<i>n</i> = 15)	25.2	8.0		20.2	8.2		19.9	9.6		-5.0	7.1		-5.3	8.9	
Question 7 (dozing off)	point	Active group (<i>n</i> = 15)	24.6	5.5	0.023*	21.9	8.2	0.036*	22.3	6.3	0.27	-2.7	8.9	0.002**	-2.3	7.1	0.026*
		Placebo group (<i>n</i> = 15)	18.2	8.7		24.2	4.9		22.0	8.0		6.0	7.2		3.8	5.4	
Question 8 (clearness of thought)	point	Active group (<i>n</i> = 15)	20.8	7.0	0.75	21.0	6.8	0.49	20.5	6.9	0.29	0.2	8.7	0.69	-0.3	7.4	0.49
		Placebo group (<i>n</i> = 15)	19.9	7.4		18.9	6.6		17.5	8.6		-1.0	8.8		-2.4	8.2	
Question 9 (nightmares)	point	Active group (<i>n</i> = 15)	24.2	6.8	0.84	25.7	4.7	0.48	24.1	6.2	0.12	1.5	4.3	0.50	-0.1	4.8	0.18
		Placebo group (<i>n</i> = 15)	23.7	5.9		26.4	3.2		25.9	5.3		2.7	5.0		2.2	4.0	
Question 10 (quality of sleep)	point	Active group (<i>n</i> = 15)	17.5	8.2	0.98	18.9	6.7	0.81	19.8	6.2	0.30	1.5	5.4	0.86	2.3	8.9	0.40
		Placebo group (<i>n</i> = 15)	17.5	8.8		19.5	6.6		17.7	8.1		1.9	7.8		0.1	5.6	
Question 11 (feelings)	point	Active group (<i>n</i> = 15)	22.9	7.8	0.62	22.5	7.4	0.83	23.9	5.0	0.23	-0.4	11.2	0.87	0.9	8.2	0.21
		Placebo group (<i>n</i> = 15)	24.2	6.0		23.3	6.8		21.1	6.7		-0.9	7.6		-3.1	7.1	
Question 12 (dreaming)	point	Active group (<i>n</i> = 15)	19.3	9.5	0.78	20.0	8.9	0.66	18.8	9.1	0.43	0.7	9.1	0.78	-0.5	10.9	0.56
		Placebo group (<i>n</i> = 15)	20.2	7.4		21.7	8.3		21.5	9.2		1.5	6.3		1.3	7.5	
Question 13 (waking at night)	point	Active group (<i>n</i> = 15)	20.9	8.4	0.44	20.2	6.6	0.13	22.5	7.3	0.91	-0.7	6.1	0.45	1.6	6.0	0.70
		Placebo group (<i>n</i> = 15)	22.9	5.4		24.1	4.4		23.5	5.5		1.2	6.5		0.7	7.9	
Question 14 (answering ability)	point	Active group (<i>n</i> = 15)	23.7	6.9	0.51	21.5	6.9	0.83	19.5	6.6	0.59	-2.3	7.6	0.98	-4.3	6.9	0.46
		Placebo group (<i>n</i> = 15)	22.2	5.5		20.0	7.5		19.8	8.6		-2.2	6.5		-2.4	6.0	
Question 15 (sleeping time)	point	Active group (<i>n</i> = 15)	21.3	5.4	0.65	22.6	5.9	0.15	23.9	7.6	0.08	1.3	5.5	0.13	2.5	8.2	0.07
		Placebo group (<i>n</i> = 15)	22.4	7.2		19.8	6.8		20.3	8.8		-2.6	7.8		-2.1	5.6	
Question 16 (deepness of sleep)	point	Active group (<i>n</i> = 15)	20.3	6.0	0.60	19.8	6.7	0.35	21.7	7.7	0.51	-0.5	8.6	0.28	1.4	9.4	0.81
		Placebo group (<i>n</i> = 15)	19.0	7.8		21.5	6.6		19.7	5.8		2.5	5.4		0.7	6.8	

The data are presented as the mean and standard deviation (SD). The baseline (Scr) values are evaluated using Student's *t*-test, the measured values are evaluated using Post-hoc comparisons with linear mixed model, with the baseline values utilized as covariates and time, group, group–time interaction, and subject as factors, and the changes are evaluated using Post-hoc comparisons with linear mixed model, with time, group, group–time interaction, and subject as factors.

** $P < 0.01$ and * $P < 0.05$ vs. the placebo group.

Appendix 3-1. The results of the safety evaluation (physical examination).

		Scr		4wks		8wks		P value		
		Mean	SD	Mean	SD	Mean	SD	Scr	4wks	8wks
Body weight (kg)	Active group (<i>n</i> = 33)	73.8	13.4	73.8	13.4	73.7	13.7	0.28	0.87	0.95
	Placebo group (<i>n</i> = 33)	70.7	9.4	70.7	9.7	70.5	9.8			
BMI (kg/m ²)	Active group (<i>n</i> = 33)	25.3	3.8	25.3	3.9	25.2	3.9	0.49	0.86	0.93
	Placebo group (<i>n</i> = 33)	24.7	2.7	24.8	2.8	24.6	2.9			
Body fat percentage (%)	Active group (<i>n</i> = 33)	26.4	7.3	26.0	7.7	26.1	7.9	0.56	0.93	0.63
	Placebo group (<i>n</i> = 33)	25.4	6.3	25.2	6.4	24.9	6.3			
Systolic blood pressure (mmHg)	Active group (<i>n</i> = 33)	122.4	12.4	123.3	10.6	124.4	15.0	0.69	0.54	0.62
	Placebo group (<i>n</i> = 33)	123.6	12.2	122.9	13.2	123.9	12.9			
Diastolic blood pressure (mmHg)	Active group (<i>n</i> = 33)	82.6	10.3	81.2	9.2	82.5	12.1	0.99	0.53	0.33
	Placebo group (<i>n</i> = 33)	82.7	10.1	80.2	10.4	80.6	9.8			
Pulse rate (bpm)	Active group (<i>n</i> = 33)	79.0	14.5	76.5	12.2	74.8	10.9	0.11	0.53	0.52
	Placebo group (<i>n</i> = 33)	74.2	8.3	75.1	10.8	73.4	8.9			
Temperature (°C)	Active group (<i>n</i> = 33)	34.9	1.3	33.7	0.6	33.7	1.0	0.51	0.07	0.73
	Placebo group (<i>n</i> = 33)	35.1	1.1	34.0	0.4	33.7	0.7			

The data are presented as the mean and standard deviation (SD). The baseline (Scr) values are evaluated using Student's *t*-test, the measured values are evaluated using the post hoc of the repeated measures ANCOVA, and the changes are evaluated using the post hoc of the repeated measures ANOVA for the between-group comparisons.

Appendix 3-2. The results of the safety evaluation (physical examination).

	Reference range		Scr		4wks		8wks		<i>P</i> value		
			Within the reference range	Outside the reference range	Within the reference range	Outside the reference range	Within the reference range	Outside the reference range	Scr	4wks	8wks
Protein	-	Active group (<i>n</i> = 33)	29	4	29	4	29	4	0.11	1.00	0.36
		Placebo group (<i>n</i> = 33)	33	0	29	3	32	1			
Glucose	-	Active group (<i>n</i> = 33)	33	0	33	0	33	0	N.A.	N.A.	N.A.
		Placebo group (<i>n</i> = 33)	33	0	32	0	33	0			
Urobilinogen	±	Active group (<i>n</i> = 33)	33	0	32	1	33	0	N.A.	1.00	N.A.
		Placebo group (<i>n</i> = 33)	33	0	32	0	33	0			
Bilirubin	-	Active group (<i>n</i> = 33)	33	0	33	0	33	0	N.A.	N.A.	N.A.
		Placebo group (<i>n</i> = 33)	33	0	32	0	33	0			
pH	5.0-7.5	Active group (<i>n</i> = 33)	32	1	33	0	32	1	1.00	N.A.	1.00
		Placebo group (<i>n</i> = 33)	33	0	32	0	32	1			
Occult blood	-	Active group (<i>n</i> = 33)	30	3	29	4	31	2	1.00	0.36	1.00
		Placebo group (<i>n</i> = 33)	31	2	31	1	31	2			
Ketone bodies	-	Active group (<i>n</i> = 33)	33	0	33	0	33	0	1.00	N.A.	1.00
		Placebo group (<i>n</i> = 33)	32	1	32	0	32	1			

The data are presented as the number of subjects within/outside the reference range and evaluated using the chi-square test.

N.A.: Not Available.

Appendix 3-3. The results of the safety evaluation (blood test).

	Reference value		Scr		4wks		8wks		P value		
			Mean	SD	Mean	SD	Mean	SD	Scr	4wks	8wks
Leukocyte count (/μL)	3300-9000	Active group (n = 33)	6327.3	2004.4	5369.7	1276.1	5297.0	1221.3	0.32	0.08	0.003**
		Placebo group (n = 33)	5933.3	1074.6	5637.5	995.7	5966.7	1443.0			
Erythrocyte count (×10 ⁴ /μL)	Male: 430-570	Active group (n = 33)	494.6	37.8	486.3	42.8	484.5	41.8	0.60	0.65	0.09
	female: 380-500	Placebo group (n = 33)	489.5	40.8	485.1	35.9	488.1	38.5			
Hemoglobin (g/dL)	Male: 13.5-17.5	Active group (n = 33)	15.4	1.2	15.1	1.4	15.0	1.4	0.17	0.64	0.16
	female: 11.5-15.0	Placebo group (n = 33)	15.0	1.2	14.9	1.2	14.9	1.1			
Hematocrit Value (%)	Male: 39.7-52.4	Active group (n = 33)	46.5	3.2	46.6	3.6	46.3	3.8	0.26	0.81	0.07
	female: 34.8-45.0	Placebo group (n = 33)	45.6	3.0	46.1	3.0	46.4	2.9			
Platelet count (×10 ⁴ /μL)	14.0-34.0	Active group (n = 33)	27.6	5.7	26.9	5.3	26.6	5.1	0.90	0.77	0.44
		Placebo group (n = 33)	27.8	6.0	27.1	5.9	27.2	6.1			
MCV (fl)	85-102	Active group (n = 33)	94.0	3.3	96.1	4.2	95.8	4.1	0.70	0.45	0.82
		Placebo group (n = 33)	93.5	6.3	95.2	6.5	95.4	6.7			
MCH (pg)	28.0-34.0	Active group (n = 33)	31.2	1.3	31.2	1.4	31.0	1.3	0.36	0.97	0.68
		Placebo group (n = 33)	30.8	2.5	30.8	2.6	30.6	2.5			
MCHC (%)	30.2-35.1	Active group (n = 33)	33.2	0.9	32.5	1.0	32.4	0.9	0.26	0.96	0.34
		Placebo group (n = 33)	32.9	1.1	32.3	1.1	32.1	1.0			
Percentage of neutrophils (%)	40.0-75.0	Active group (n = 33)	57.8	8.0	54.9	7.8	53.2	7.9	0.51	0.42	0.040*
		Placebo group (n = 33)	56.4	9.1	55.4	7.9	55.6	8.3			
Percentage of lymphocytes (%)	18.0-49.0	Active group (n = 33)	33.8	7.3	35.6	7.3	37.1	7.6	0.79	0.66	0.09
		Placebo group (n = 33)	34.3	8.4	35.3	7.2	35.1	7.8			

Percentage of monocytes (%)	2.0-10.0	Active group (n = 33)	5.0	1.3	5.1	1.3	5.5	1.3	0.018*	0.74	0.07
		Placebo group (n = 33)	5.8	1.4	5.4	1.3	5.5	1.1			
Percentages of eosinophils (%)	0.0-8.0	Active group (n = 33)	2.8	1.9	3.6	2.3	3.5	2.4	0.95	0.22	0.41
		Placebo group (n = 33)	2.9	1.9	3.2	2.1	3.1	2.4			
Percentages of basophils (%)	0.0-2.0	Active group (n = 33)	0.6	0.4	0.8	0.5	0.7	0.5	0.61	0.14	0.67
		Placebo group (n = 33)	0.7	0.4	0.7	0.4	0.7	0.4			
Neutrophils (/μL)	-	Active group (n = 33)	3739.4	1509.2	2998.9	911.0	2871.5	910.4	0.26	0.15	0.006**
		Placebo group (n = 33)	3382.8	984.0	3146.7	807.5	3340.3	1059.3			
Lymphocytes (/μL)	-	Active group (n = 33)	2071.3	612.8	1869.8	472.2	1919.9	448.6	0.61	0.10	0.039*
		Placebo group (n = 33)	2001.5	500.8	1967.3	429.7	2073.9	582.4			
Monocytes (/μL)	-	Active group (n = 33)	310.4	117.5	267.6	80.1	289.6	90.1	0.29	0.19	0.28
		Placebo group (n = 33)	337.5	87.3	304.9	104.6	325.8	100.8			
Eosinophils (/μL)	-	Active group (n = 33)	170.2	110.0	195.5	141.0	180.1	137.0	0.99	0.47	0.90
		Placebo group (n = 33)	170.7	119.4	180.3	129.3	183.8	139.7			
Basophils (/μL)	-	Active group (n = 33)	35.9	15.5	38.0	18.9	35.8	22.5	0.29	0.37	0.55
		Placebo group (n = 33)	40.9	22.2	38.3	20.2	42.9	25.9			
ALP (U/L)	100-325	Active group (n = 33)	223.2	81.3	218.6	80.0	213.8	80.0	0.70	0.63	0.85
		Placebo group (n = 33)	216.3	60.4	213.3	47.4	209.1	46.8			
LD (LDH) (U/L)	120-240	Active group (n = 33)	194.6	28.6	192.5	30.1	193.5	31.7	0.24	0.91	0.38
		Placebo group (n = 33)	186.6	26.3	186.3	27.1	189.2	26.8			
LAP (U/L)	Male: 45-81	Active group (n = 33)	65.2	14.2	66.2	15.9	65.7	15.5	0.21	0.67	0.94
	female: 37-61	Placebo group (n = 33)	60.9	13.3	61.1	15.9	61.7	12.7			
	0.2-1.2	Active group (n = 33)	0.9	0.5	0.8	0.4	0.9	0.4	0.80	0.44	0.66

Total bilirubin (mg/dL)		Placebo group (n = 33)	0.9	0.3	0.9	0.4	0.9	0.4			
Direct bilirubin (mg/dL)	0.0-0.2	Active group (n = 33)	0.1	0.1	0.1	0.1	0.1	0.1	0.40	0.27	0.44
		Placebo group (n = 33)	0.1	0.1	0.1	0.0	0.1	0.1			
Indirect bilirubin (mg/dL)	0.2-1.0	Active group (n = 33)	0.8	0.4	0.7	0.3	0.8	0.4	0.89	0.32	0.78
		Placebo group (n = 33)	0.8	0.2	0.8	0.3	0.8	0.3			
Direct bilirubin/ Indirect bilirubin ratio	-	Active group (n = 33)	0.1	0.1	0.2	0.1	0.2	0.1			
		Placebo group (n = 33)	0.1	0.1	0.1	0.1	0.1	0.1	0.20	0.14	0.88
Cholinesterase (ChE) (U/L)	Male: 234-493 female: 200-452	Active group (n = 33)	386.0	81.9	372.3	80.0	373.1	86.6			
		Placebo group (n = 33)	371.2	54.2	362.8	51.7	361.3	48.7	0.39	0.90	0.82
Total protein (g/dL)	6.7-8.3	Active group (n = 33)	7.4	0.4	7.3	0.4	7.3	0.5			
		Placebo group (n = 33)	7.3	0.4	7.3	0.4	7.3	0.4	0.66	0.68	0.16
Urea nitrogen (mg/dL)	8.0-20.0	Active group (n = 33)	14.6	3.9	13.7	3.0	14.1	3.5			
		Placebo group (n = 33)	13.9	3.7	13.1	4.5	13.3	4.1	0.47	0.92	0.64
Creatinine (mg/dL)	Male: 0.61-1.04 female: 0.47-0.79	Active group (n = 33)	0.8	0.1	0.8	0.1	0.8	0.1			
		Placebo group (n = 33)	0.8	0.1	0.8	0.1	0.8	0.1	0.42	0.72	0.09
Uric acid (mg/dL)	Male: 3.8-7.0 female: 2.5-7.0	Active group (n = 33)	6.1	1.5	6.0	1.6	6.0	1.5			
		Placebo group (n = 33)	6.1	1.1	6.2	1.3	6.1	1.3	0.99	0.21	0.43
CK (U/l)	Male: 60-270 female: 40-150	Active group (n = 33)	143.3	88.5	133.8	87.6	122.2	51.5			
		Placebo group (n = 33)	122.1	57.9	111.1	50.2	132.9	73.8	0.25	0.36	0.24
Sodium (mEq/L)	137-147	Active group (n = 33)	140.7	1.6	141.0	2.0	141.0	1.7			
		Placebo group (n = 33)	140.1	1.3	140.8	1.4	140.5	1.5	0.09	0.94	0.54

Potassium (mEq/L)	3.5-5.0	Active group (<i>n</i> = 33)	4.1	0.3	4.0	0.4	4.0	0.3	0.60	0.60	0.71
		Placebo group (<i>n</i> = 33)	4.1	0.4	4.0	0.4	4.0	0.4			
Chloride (mEq/L)	98-108	Active group (<i>n</i> = 33)	100.5	2.0	100.9	2.3	101.0	2.3	0.15	0.81	0.50
		Placebo group (<i>n</i> = 33)	99.8	1.5	100.6	2.4	100.3	2.2			
Calcium (mEq/L)	8.4-10.4	Active group (<i>n</i> = 33)	9.5	0.3	9.3	0.3	9.4	0.3	0.80	0.42	0.44
		Placebo group (<i>n</i> = 33)	9.4	0.3	9.3	0.3	9.3	0.4			
Inorganic phosphorus (mEq/L)	2.5-4.5	Active group (<i>n</i> = 33)	3.4	0.5	3.5	0.6	3.5	0.5	0.96	0.50	0.26
		Placebo group (<i>n</i> = 33)	3.4	0.5	3.5	0.6	3.6	0.8			
Serum iron (µg/dL)	Male: 50-200	Active group (<i>n</i> = 33)	126.9	37.6	114.5	31.4	121.2	31.1	0.84	0.93	0.10
	female: 40-180	Placebo group (<i>n</i> = 33)	129.1	48.3	114.8	40.7	108.5	31.9			
Serum amylase (U/L)	40-122	Active group (<i>n</i> = 33)	73.5	27.8	73.4	27.0	73.5	29.1	0.89	0.60	0.36
		Placebo group (<i>n</i> = 33)	72.7	18.6	70.9	16.8	70.6	17.7			
Total cholesterol (mg/dL)	120-219	Active group (<i>n</i> = 33)	226.8	34.1	220.3	29.8	216.9	33.9	0.80	0.65	0.62
		Placebo group (<i>n</i> = 33)	224.5	40.5	216.5	38.5	217.6	39.4			
HDL cholesterol (mg/dL)	Male: 40-85	Active group (<i>n</i> = 33)	64.6	19.4	60.2	16.4	59.7	17.5	0.12	0.20	0.07
	female: 40-95	Placebo group (<i>n</i> = 33)	57.6	16.4	55.8	16.4	58.2	19.7			
LDL cholesterol (mg/dL)	65-139	Active group (<i>n</i> = 33)	139.6	32.1	135.2	30.5	133.1	33.0	0.62	0.22	0.62
		Placebo group (<i>n</i> = 33)	135.3	38.0	127.2	36.2	127.2	36.3			
Triglyceride (mg/dL)	30-149	Active group (<i>n</i> = 33)	125.2	63.6	142.7	140.7	126.0	70.1	0.006**	0.48	0.19
		Placebo group (<i>n</i> = 33)	188.0	109.8	222.2	203.4	196.2	141.2			
Glucose (mg/dL)	70-109	Active group (<i>n</i> = 33)	88.2	11.6	89.6	8.3	90.1	8.3	0.71	0.06	0.72
		Placebo group (<i>n</i> = 33)	89.2	11.7	93.9	12.0	91.3	11.2			

HbA1c (NGSP) (%)	4.6-6.2	Active group (n = 33)	5.3	0.3	5.3	0.3	5.3	0.3	0.41	0.28	1.00
		Placebo group (n = 33)	5.4	0.4	5.3	0.4	5.4	0.4			
Glycoalbumin (%)	12.3-16.5	Active group (n = 33)	13.1	1.3	13.3	1.3	13.2	1.5	0.56	0.53	0.50
		Placebo group (n = 33)	12.8	1.6	13.2	1.6	13.1	1.5			

The data are presented as the mean and standard deviation (SD). The baseline (Scr) values are evaluated using Student's *t*-test, the measured values are evaluated using the post hoc of the repeated measures ANCOVA, and the changes are evaluated using the post hoc of the repeated measures ANOVA for the between-group comparisons.

***P* < 0.01 and **P* < 0.05 vs. the placebo group.