

Effect of rovatirelin in patients with cerebellar ataxia: two randomised double-blind placebo-controlled phase 3 trials

SUPPLEMENTARY MATERIALS

Supplementary table 1 Baseline characteristics of the KPS1301 study subgroup*

full analysis set

	Placebo (N=44)	Rovatirelin 2.4 mg (N=46)
Age, years	63.2 ± 11.4	65.2 ± 9.5
Sex, n (%)		
Male	28 (63.6)	24 (52.2)
Female	16 (36.4)	22 (47.8)
Disease duration, years	11.9 ± 6.3	13.6 ± 8.8
Type of SCA, n (%)		
SCA6	22 (50.0)	20 (43.5)
SCA31	8 (18.2)	7 (15.2)
CCA	14 (31.8)	19 (41.3)
SARA total score, points	16.80 ± 2.94	16.93 ± 4.49
<15, n (%)	11 (25.0)	14 (30.4)
≥15, n (%)	33 (75.0)	32 (69.6)

Data are presented as mean ± SD unless stated otherwise.

*KPS1301 subgroup included patients who met KPS1305 inclusion criteria (SARA gait score of 2–6; stance score of ≥2; finger chase, nose-finger test, and fast alternating hand movement scores of ≥1 each)

CCA, cortical cerebellar atrophy; SARA, Scale for Assessment and Rating of Ataxia; SCA, spinocerebellar ataxia; SD, standard deviation

Supplementary table 2 Endocrinology test results in the KPS1301 study

(A) Thyroid stimulating hormone, mIU/L

	Placebo (N=123)	Rovatiirelin 1.6 mg (N=125)	Rovatiirelin 2.4 mg (N=126)
Week -4, n	123	125	126
Mean \pm SD	2.79 \pm 2.78	3.14 \pm 3.25	4.40 \pm 9.52
Median (range)	2.05 (0.14–20.40)	2.22 (0.15–19.80)	2.44 (0.01–100.00)
Week 0, n	123	125	126
Mean \pm SD	2.18 \pm 1.67	2.66 \pm 3.37	3.73 \pm 8.63
Median (range)	1.71 (0.08–11.10)	1.99 (0.12–35.90)	1.99 (0.01–71.00)
Week 4, n	123	124	124
Mean \pm SD	2.28 \pm 1.62	6.01 \pm 9.69	7.08 \pm 11.21
Median (range)	1.87 (0.12–9.68)	3.70 (0.48–100.00)	4.17 (0.01–79.40)
Week 8, n	122	120	117
Mean \pm SD	2.21 \pm 1.50	5.79 \pm 9.81	6.82 \pm 11.52
Median (range)	1.83 (0.40–9.29)	3.65 (0.26–100.00)	4.42 (0.10–100.00)
Week 12, n	122	118	112
Mean \pm SD	2.06 \pm 1.14	5.79 \pm 10.12	6.86 \pm 12.34
Median (range)	1.74 (0.39–6.44)	3.42 (0.62–100.00)	3.85 (0.07–100.00)
Week 16, n	120	116	108
Mean \pm SD	2.08 \pm 1.41	5.41 \pm 9.62	6.16 \pm 10.58
Median (range)	1.70 (0.29–9.06)	3.51 (0.38–100.00)	3.99 (0.23–100.00)
Week 20, n	120	113	106
Mean \pm SD	2.11 \pm 1.45	5.50 \pm 8.55	5.94 \pm 9.48
Median (range)	1.80 (0.30–11.10)	3.67 (0.57–86.20)	3.68 (0.41–84.70)
Week 24, n	119	106	103
Mean \pm SD	2.07 \pm 1.39	4.57 \pm 4.45	6.05 \pm 10.77
Median (range)	1.79 (0.40–11.60)	3.49 (0.48–36.10)	3.70 (0.41–100.00)
Week 28, n	118	105	102
Mean \pm SD	2.13 \pm 1.78	4.67 \pm 3.40	6.01 \pm 9.92
Median (range)	1.73 (0.05–13.80)	3.46 (0.64–15.60)	4.06 (0.11–95.80)
Final evaluation, n	123	124	125
Mean \pm SD	2.12 \pm 1.75	5.71 \pm 8.59	5.68 \pm 9.11
Median (range)	1.73 (0.05–13.80)	3.54 (0.42–86.20)	3.90 (0.11–95.80)
Follow-up visit, n	15	24	28
Mean \pm SD	2.52 \pm 1.89	7.54 \pm 19.85	3.50 \pm 5.15
Median (range)	1.73 (0.01–5.92)	2.89 (0.07–100.00)	1.93 (0.24–26.50)

SD, standard deviation

(B) Free triiodothyronine, ng/L

	Placebo (N=123)	Rovatirolin 1.6 mg (N=125)	Rovatirolin 2.4 mg (N=126)
Week -4, n	123	125	126
Mean ± SD	3.21 ± 0.40	3.25 ± 0.51	3.24 ± 0.48
Median (range)	3.21 (2.46–4.05)	3.22 (2.02–5.88)	3.17 (2.06–5.49)
Week 0, n	123	125	126
Mean ± SD	2.88 ± 0.34	2.87 ± 0.39	2.85 ± 0.35
Median (range)	2.86 (2.27–3.66)	2.84 (2.11–3.98)	2.81 (1.88–4.54)
Week 4, n	123	124	124
Mean ± SD	2.95 ± 0.32	4.02 ± 0.69	4.21 ± 0.70
Median (range)	2.99 (2.27–3.80)	3.96 (2.17–6.32)	4.19 (2.34–6.50)
Week 8, n	122	120	117
Mean ± SD	2.94 ± 0.35	4.02 ± 0.68	4.10 ± 0.70
Median (range)	2.95 (2.23–3.85)	3.94 (2.33–6.33)	4.02 (2.75–7.54)
Week 12, n	122	118	112
Mean ± SD	2.88 ± 0.35	3.90 ± 0.66	4.01 ± 0.62
Median (range)	2.88 (2.12–3.77)	3.86 (2.41–6.30)	3.92 (2.84–6.12)
Week 16, n	120	116	108
Mean ± SD	2.87 ± 0.36	3.87 ± 0.65	3.95 ± 0.72
Median (range)	2.84 (1.85–3.88)	3.8 (2.49–5.95)	3.82 (2.30–6.65)
Week 20, n	120	113	106
Mean ± SD	2.93 ± 0.38	3.93 ± 0.57	3.97 ± 0.61
Median (range)	2.9 (2.19–4.26)	3.93 (2.56–6.21)	3.90 (2.60–5.83)
Week 24, n	119	106	103
Mean ± SD	2.97 ± 0.37	4.00 ± 0.62	4.02 ± 0.67
Median (range)	2.96 (2.12–3.96)	3.94 (2.47–5.84)	3.93 (2.59–5.69)
Week 28, n	118	105	102
Mean ± SD	2.97 ± 0.42	4.01 ± 0.66	4.01 ± 0.74
Median (range)	2.94 (2.23–5.18)	3.95 (2.46–7.42)	3.89 (2.47–7.41)
Final evaluation, n	123	124	125
Mean ± SD	2.96 ± 0.42	3.99 ± 0.68	4.02 ± 0.77
Median (range)	2.93 (2.23–5.18)	3.95 (2.46–7.42)	3.9 (2.34–7.41)
Follow-up visit, n	15	24	28
Mean ± SD	3.58 ± 1.48	2.97 ± 0.54	3.08 ± 0.50
Median (range)	3.30 (2.46–8.76)	3.00 (1.62–4.1)	2.98 (2.15–4.38)

SD, standard deviation

(C) Free thyroxine, ng/dL

	Placebo (N=123)	Rovatiirelin 1.6 mg (N=125)	Rovatiirelin 2.4 mg (N=126)
Week -4, n	123	125	126
Mean ± SD	1.36 ± 0.20	1.39 ± 0.20	1.34 ± 0.23
Median (range)	1.34 (0.91–1.92)	1.37 (0.97–1.93)	1.35 (0.73–2.26)
Week 0, n	123	125	126
Mean ± SD	1.19 ± 0.18	1.22 ± 0.18	1.18 ± 0.21
Median (range)	1.17 (0.80–1.81)	1.20 (0.80–1.79)	1.17 (0.54–1.85)
Week 4, n	123	124	124
Mean ± SD	1.26 ± 0.20	1.75 ± 0.28	1.80 ± 0.34
Median (range)	1.26 (0.83–2.14)	1.76 (0.77–2.57)	1.80 (0.69–2.78)
Week 8, n	122	120	117
Mean ± SD	1.28 ± 0.17	1.77 ± 0.28	1.77 ± 0.30
Median (range)	1.27 (0.88–1.76)	1.76 (0.70–2.52)	1.74 (1.00–2.75)
Week 12, n	122	118	112
Mean ± SD	1.26 ± 0.17	1.74 ± 0.27	1.75 ± 0.29
Median (range)	1.27 (0.86–1.81)	1.72 (0.80–2.49)	1.71 (0.92–2.76)
Week 16, n	120	116	108
Mean ± SD	1.27 ± 0.18	1.73 ± 0.26	1.75 ± 0.31
Median (range)	1.27 (0.93–1.86)	1.77 (0.88–2.31)	1.74 (0.95–2.67)
Week 20, n	120	113	106
Mean ± SD	1.29 ± 0.18	1.77 ± 0.25	1.78 ± 0.30
Median (range)	1.28 (0.92–1.87)	1.80 (0.84–2.32)	1.80 (0.79–2.47)
Week 24, n	119	106	103
Mean ± SD	1.33 ± 0.18	1.80 ± 0.27	1.81 ± 0.29
Median (range)	1.31 (0.95–1.78)	1.83 (1.10–2.47)	1.79 (0.76–2.53)
Week 28, n	118	105	102
Mean ± SD	1.30 ± 0.19	1.77 ± 0.24	1.76 ± 0.27
Median (range)	1.29 (0.96–2.30)	1.78 (1.12–2.29)	1.73 (1.09–2.45)
Final evaluation, n	123	124	125
Mean ± SD	1.30 ± 0.19	1.75 ± 0.26	1.77 ± 0.30
Median (range)	1.28 (0.96–2.30)	1.76 (0.84–2.29)	1.76 (0.98–2.67)
Follow-up visit, n	15	24	28
Mean ± SD	1.60 ± 0.66	1.31 ± 0.24	1.32 ± 0.31
Median (range)	1.49 (1.06–3.84)	1.29 (0.72–1.78)	1.28 (0.86–1.99)

SD, standard deviation

(D) Prolactin in men, $\mu\text{g/L}$

	Placebo (N=67)	Rovatrelin 1.6 mg (N=64)	Rovatrelin 2.4 mg (N=65)
Week -4, n	67	64	65
Mean \pm SD	8.90 \pm 3.32	11.76 \pm 8.66	29.40 \pm 161.90
Median (range)	8.46 (3.32–16.42)	9.97 (2.84–63.32)	7.97 (3.10–1313.00)
Week 0, n	67	64	65
Mean \pm SD	8.80 \pm 3.82	9.25 \pm 4.04	29.81 \pm 166.14
Median (range)	8.00 (3.28–23.01)	8.37 (3.82–27.19)	7.59 (3.58–1347.00)
Week 4, n	67	64	64
Mean \pm SD	8.45 \pm 4.08	20.00 \pm 8.58	35.43 \pm 144.87
Median (range)	7.52 (2.69–29.59)	18.10 (4.61–52.42)	14.95 (7.44–1174.00)
Week 8, n	66	60	61
Mean \pm SD	8.43 \pm 3.19	20.56 \pm 11.56	36.60 \pm 145.54
Median (range)	7.96 (3.20–23.14)	18.94 (3.60–86.46)	16.69 (3.93–1152.00)
Week 12, n	67	60	59
Mean \pm SD	8.61 \pm 4.17	21.99 \pm 12.96	35.80 \pm 135.69
Median (range)	7.57 (4.12–28.81)	19.09 (7.50–98.31)	15.62 (3.71–1056.00)
Week 16, n	66	59	57
Mean \pm SD	9.91 \pm 6.00	22.56 \pm 13.79	36.73 \pm 140.75
Median (range)	7.92 (3.85–34.44)	20.74 (5.04–82.02)	16.96 (4.1–1078.00)
Week 20, n	66	56	55
Mean \pm SD	9.15 \pm 3.79	21.61 \pm 12.60	36.43 \pm 131.61
Median (range)	8.24 (3.09–26.73)	19.07 (5.88–82.64)	16.29 (4.30–991.20)
Week 24, n	65	55	53
Mean \pm SD	9.31 \pm 3.53	24.32 \pm 23.50	37.1263 \pm 144.47
Median (range)	8.84 (2.95–19.55)	18.94 (6.55–170.8)	15.95 (3.64–1067.00)
Week 28, n	65	55	53
Mean \pm SD	8.93 \pm 3.80	22.22 \pm 15.74	35.36 \pm 125.36
Median (range)	8.21 (3.65–22.61)	17.44 (6.19–102.10)	16.00 (5.40–928.30)
Final evaluation, n	67	64	64
Mean \pm SD	8.86 \pm 3.77	21.64 \pm 15.03	31.85 \pm 114.20
Median (range)	8.19 (3.65–22.61)	17.4 (5.09–102.10)	15.91 (3.93–928.30)
Follow-up visit, n	6	12	15
Mean \pm SD	11.31 \pm 10.27	10.14 \pm 3.90	8.57 \pm 2.93
Median (range)	6.60 (3.56–30.14)	11.02 (3.80–16.92)	7.97 (3.83–13.93)

SD, standard deviation

(E) Prolactin in women, µg/L

	Placebo (N=56)	Rovatiirelin 1.6 mg (N=61)	Rovatiirelin 2.4 mg (N=61)
Week -4, n	56	61	61
Mean ± SD	13.00 ± 22.78	13.15 ± 17.36	12.10 ± 7.10
Median (range)	8.98 (2.83–176.30)	10.02 (3.95–139.90)	10.60 (2.76–47.03)
Week 0, n	56	61	61
Mean ± SD	11.81 ± 21.98	9.27 ± 4.50	8.56 ± 2.89
Median (range)	8.22 (3.81–171.00)	7.85 (4.07–28.07)	8.23 (3.91–15.46)
Week 4, n	56	60	60
Mean ± SD	10.72 ± 15.44	24.37 ± 11.58	27.41 ± 29.16
Median (range)	8.22 (3.13–120.60)	23.99 (5.96–55.61)	22.46 (6.54–230.70)
Week 8, n	56	60	56
Mean ± SD	9.06 ± 8.28	24.41 ± 10.59	28.00 ± 29.76
Median (range)	7.85 (3.19–64.44)	23.48 (6.54–51.81)	23.23 (7.86–230.30)
Week 12, n	55	58	53
Mean ± SD	9.53 ± 7.69	24.80 ± 10.17	26.85 ± 23.81
Median (range)	8.09 (3.79–55.08)	23.80 (6.77–55.55)	19.96 (6.82–170.70)
Week 16, n	54	57	51
Mean ± SD	11.11 ± 22.95	25.27 ± 11.02	25.69 ± 11.21
Median (range)	7.05 (2.70–174.50)	23.74 (7.08–55.98)	24.67 (6.45–71.44)
Week 20, n	54	57	51
Mean ± SD	10.42 ± 17.95	24.25 ± 9.37	28.31 ± 28.31
Median (range)	7.64 (3.50–138.40)	22.47 (9.02–58.32)	23.01 (8.11–211.30)
Week 24, n	54	51	50
Mean ± SD	10.28 ± 11.54	25.20 ± 11.45	24.69 ± 9.86
Median (range)	7.53 (2.95–73.26)	22.46 (10.23–58.43)	23.80 (9.96–58.87)
Week 28, n	53	50	49
Mean ± SD	10.00 ± 11.58	23.92 ± 0.97	26.40 ± 11.88
Median (range)	7.57 (3.98–88.04)	21.56 (7.15–57.86)	24.42 (4.22–61.26)
Final evaluation, n	56	60	61
Mean ± SD	9.80 ± 11.32	23.38 ± 10.96	27.77 ± 26.57
Median (range)	7.41 (3.98–88.04)	21.56 (6.33–57.86)	24.02 (4.22–211.3)
Follow-up visit, n	9	12	13
Mean ± SD	20.24 ± 31.86	13.12 ± 5.88	11.70 ± 3.73
Median (range)	10.33 (4.82–104.40)	12.13 (5.89–26.85)	10.76 (7.05–18.83)

SD, standard deviation

Supplementary table 3 Endocrinology test results in the KPS1305 study

(A) Thyroid stimulating hormone, mIU/L

	Placebo (N=102)	Rovatiirelin 2.4 mg (N=101)
Week -4, n	102	101
Mean \pm SD	4.03 \pm 10.24	2.11 \pm 1.40
Median (range)	2.02 (0.35–100)	1.77 (0.19–9.86)
Week 0, n	102	100
Mean \pm SD	3.44 \pm 9.91	1.93 \pm 1.20
Median (range)	1.90 (0.24–100.00)	1.66 (0.07–6.64)
Week 4, n	101	99
Mean \pm SD	2.77 \pm 3.87	4.13 \pm 2.68
Median (range)	1.84 (0.26–31.40)	4.02 (0.09–12.60)
Week 8, n	99	95
Mean \pm SD	3.43 \pm 8.27	4.26 \pm 3.06
Median (range)	1.95 (0.36–79.30)	3.53 (0.18–17.30)
Week 12, n	95	94
Mean \pm SD	3.38 \pm 10.18	4.18 \pm 2.60
Median (range)	1.95 (0.34–100.00)	3.78 (0.45–10.80)
Week 16, n	91	94
Mean \pm SD	3.09 \pm 7.95	3.67 \pm 2.66
Median (range)	1.84 (0.20–76.20)	3.06 (0.32–13.80)
Week 20, n	90	93
Mean \pm SD	2.75 \pm 5.07	4.11 \pm 3.27
Median (range)	1.78 (0.32–48.10)	3.27 (0.13–17.60)
Week 24, n	90	91
Mean \pm SD	3.37 \pm 10.40	4.07 \pm 2.84
Median (range)	1.86 (0.30–100.00)	3.21 (0.32–14.30)
Final evaluation, n	101	101
Mean \pm SD	3.32 \pm 9.85	3.95 \pm 2.88
Median (range)	1.95 (0.30–100.00)	3.13 (0.09–14.30)
Follow-up visit, n	100	100
Mean \pm SD	3.82 \pm 9.94	2.21 \pm 1.36
Median (range)	2.14 (0.24–100.00)	1.89 (0.04–8.21)

SD, standard deviation

(B) Free triiodothyronine, ng/L

	Placebo (N=102)	Rovatiirelin 2.4 mg (N=101)
Week -4, n	102	101
Mean \pm SD	3.10 \pm 0.47	3.24 \pm 0.43
Median (range)	3.10 (1.96–4.94)	3.22 (2.25–4.40)
Week 0, n	102	100
Mean \pm SD	2.78 \pm 0.34	2.86 \pm 0.35
Median (range)	2.74 (1.56–3.75)	2.85 (1.91–4.02)
Week 4, n	101	99
Mean \pm SD	2.87 \pm 0.33	4.40 \pm 0.77
Median (range)	2.85 (2.14–3.67)	4.32 (2.90–7.17)
Week 8, n	99	95
Mean \pm SD	2.85 \pm 0.33	4.28 \pm 0.68
Median (range)	2.82 (1.97–3.68)	4.20 (3.00–7.19)
Week 12, n	95	94
Mean \pm SD	2.90 \pm 0.34	4.40 \pm 0.82
Median (range)	2.86 (2.00–3.68)	4.33 (2.63–7.30)
Week 16, n	91	94
Mean \pm SD	2.95 \pm 0.33	4.26 \pm 0.70
Median (range)	2.97 (2.25–3.92)	4.27 (2.69–6.22)
Week 20, n	90	93
Mean \pm SD	3.01 \pm 0.35	4.26 \pm 0.61
Median (range)	3.00 (2.25–3.82)	4.20 (3.13–6.11)
Week 24, n	90	91
Mean \pm SD	3.00 \pm 0.35	4.24 \pm 0.85
Median (range)	2.99 (2.07–3.79)	4.16 (2.29–7.11)
Final evaluation, n	101	101
Mean \pm SD	2.99 \pm 0.36	4.22 \pm 0.88
Median (range)	2.97 (2.07–3.79)	4.07 (2.29–7.17)
Follow-up visit, n	100	100
Mean \pm SD	3.28 \pm 0.52	3.13 \pm 0.44
Median (range)	3.33 (2.04–4.76)	3.07 (2.11–4.26)

SD, standard deviation

(C) Free thyroxine, ng/dL

	Placebo (N=102)	Rovatiirelin 2.4 mg (N=101)
Week -4, n	102	101
Mean \pm SD	1.34 \pm 0.20	1.37 \pm 0.18
Median (range)	1.36 (0.40–1.87)	1.37 (0.93–1.90)
Week 0, n	102	100
Mean \pm SD	1.19 \pm 0.19	1.19 \pm 0.16
Median (range)	1.19 (0.32–1.72)	1.19 (0.88–1.57)
Week 4, n	101	99
Mean \pm SD	1.25 \pm 0.17	1.89 \pm 0.28
Median (range)	1.24 (0.75–1.79)	1.87 (1.31–3.28)
Week 8, n	99	95
Mean \pm SD	1.25 \pm 0.17	1.81 \pm 0.24
Median (range)	1.24 (0.67–1.78)	1.81 (1.21–2.48)
Week 12, n	95	94
Mean \pm SD	1.26 \pm 0.18	1.84 \pm 0.29
Median (range)	1.27 (0.61–1.73)	1.82 (1.20–2.59)
Week 16, n	91	94
Mean \pm SD	1.29 \pm 0.19	1.82 \pm 0.22
Median (range)	1.29 (0.74–1.82)	1.81 (1.33–2.29)
Week 20, n	90	93
Mean \pm SD	1.31 \pm 0.17	1.78 \pm 0.25
Median (range)	1.29 (0.88–1.77)	1.77 (1.18–2.43)
Week 24, n	90	91
Mean \pm SD	1.29 \pm 0.17	1.74 \pm 0.28
Median (range)	1.30 (0.68–1.77)	1.67 (1.12–2.78)
Final evaluation, n	101	101
Mean \pm SD	1.29 \pm 0.17	1.76 \pm 0.31
Median (range)	1.29 (0.68–1.77)	1.67 (1.12–3.28)
Follow-up visit, n	100	100
Mean \pm SD	1.42 \pm 0.20	1.30 \pm 0.21
Median (range)	1.44 (0.61–1.83)	1.28 (0.76–1.92)

SD, standard deviation

(D) Prolactin in men, µg/L

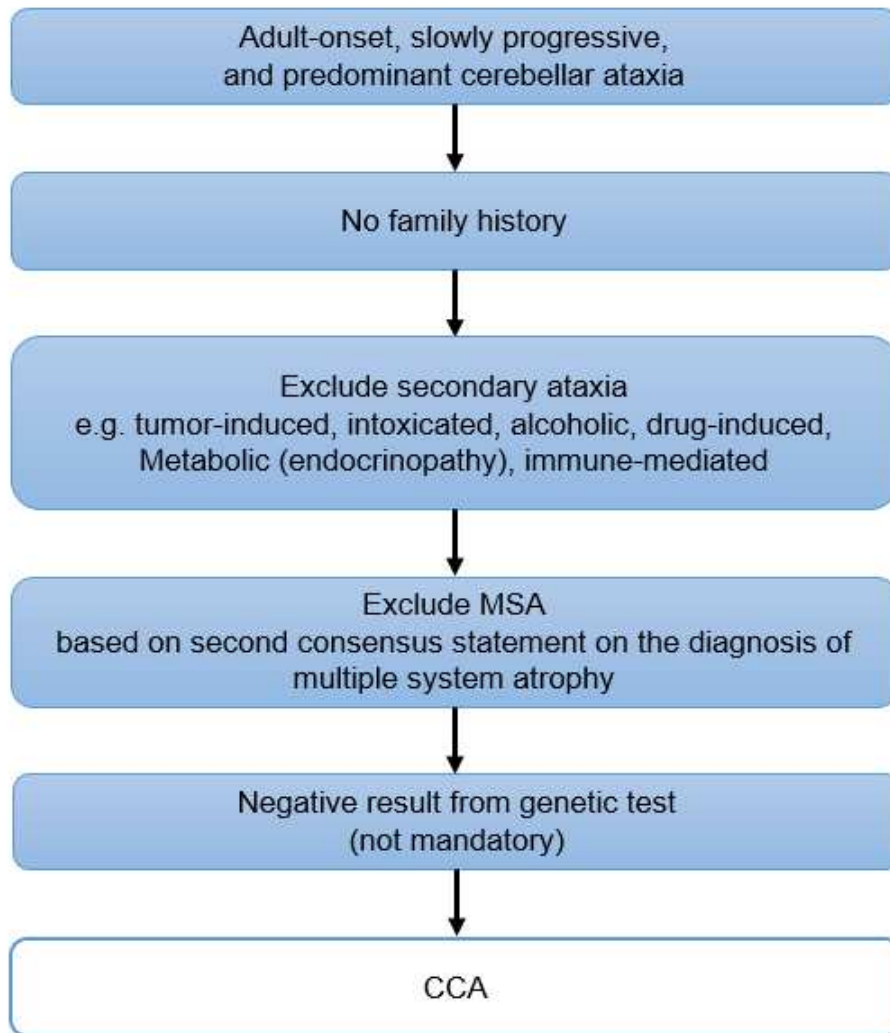
	Placebo (N=50)	Rovatiselin 2.4 mg (N=57)
Week -4, n	50	57
Mean ± SD	11.70 ± 6.61	9.54 ± 3.56
Median (range)	10.03 (4.76–41.74)	9.22 (2.61–20.09)
Week 0, n	50	57
Mean ± SD	10.97 ± 7.75	9.61 ± 4.34
Median (range)	9.04 (4.53–58.04)	8.38 (4.18–31.53)
Week 4, n	49	55
Mean ± SD	9.53 ± 3.88	21.12 ± 12.93
Median (range)	8.89 (3.86–24.13)	19.10 (7.77–93.53)
Week 8, n	48	52
Mean ± SD	11.30 ± 11.37	19.15 ± 8.36
Median (range)	4.70 (9.06–84.20)	5.92 (17.19–52.87)
Week 12, n	46	52
Mean ± SD	10.89 ± 6.79	18.86 ± 7.96
Median (range)	9.27 (4.23–48.77)	17.83 (5.21–47.06)
Week 16, n	45	52
Mean ± SD	10.07 ± 6.37	18.79 ± 6.76
Median (range)	8.83 (3.90–46.61)	17.93 (6.35–39.14)
Week 20, n	45	51
Mean ± SD	11.14 ± 7.83	17.25 ± 6.96
Median (range)	3.51 (9.12–55.35)	5.80 (14.69–34.08)
Week 24, n	45	51
Mean ± SD	10.77 ± 6.13	19.23 ± 7.97
Median (range)	9.45 (3.40–43.89)	16.7 (5.73–44.30)
Final evaluation, n	49	57
Mean ± SD	10.92 ± 6.13	18.87 ± 7.97
Median (range)	9.45 (3.40–43.89)	2.90 (16.70–44.30)
Follow-up visit, n	49	56
Mean ± SD	13.00 ± 8.71	10.40 ± 3.74
Median (range)	11.56 (3.99–59.36)	9.95 (4.12–26.74)

SD, standard deviation

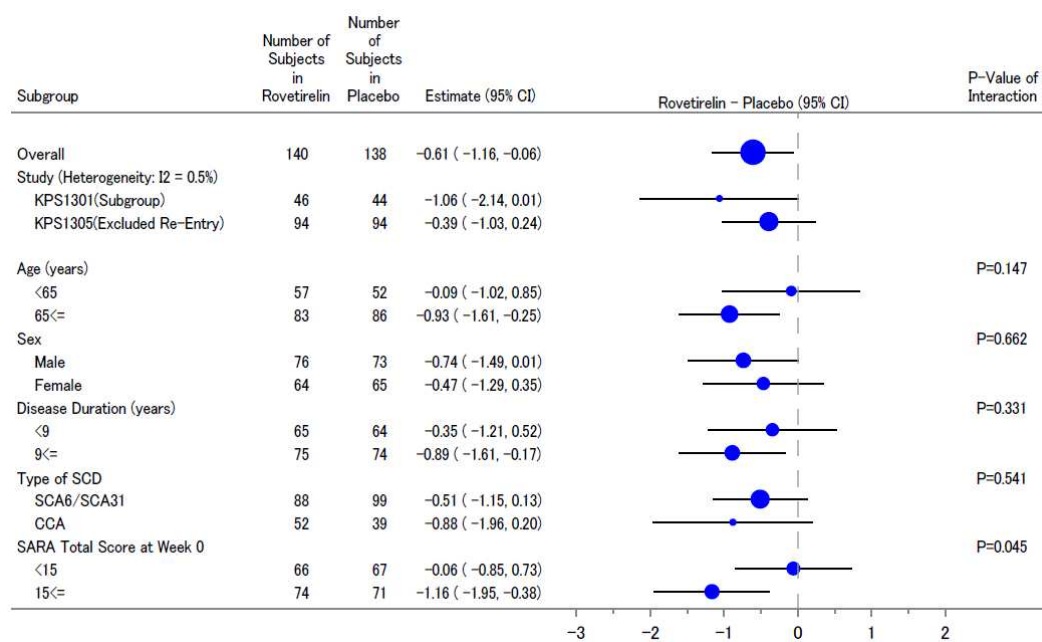
(E) Prolactin in women, µg/L

	Placebo (N=52)	Rovatiselin 2.4 mg (N=44)
Week -4, n	52	44
Mean ± SD	12.23 ± 5.48	11.42 ± 5.29
Median (range)	10.53 (5.13–30.20)	10.60 (3.34–30.61)
Week 0, n	52	43
Mean ± SD	9.96 ± 4.19	10.95 ± 4.43
Median (range)	8.69 (4.14–25.19)	9.67 (3.80–23.48)
Week 4, n	52	44
Mean ± SD	10.84 ± 4.52	25.33 ± 12.30
Median (range)	10.21 (5.35–26.14)	23.67 (6.67–74.82)
Week 8, n	51	43
Mean ± SD	10.85 ± 6.10	27.86 ± 15.85
Median (range)	9.17 (3.50–37.48)	24.67 (8.26–80.89)
Week 12, n	49	42
Mean ± SD	10.86 ± 6.34	25.68 ± 13.23
Median (range)	9.67 (5.35–47.74)	25.42 (8.76–73.05)
Week 16, n	46	42
Mean ± SD	9.65 ± 3.11	25.93 ± 15.19
Median (range)	9.69 (4.82–17.32)	22.69 (6.76–86.05)
Week 20, n	45	42
Mean ± SD	9.90 ± 3.80	24.72 ± 10.85
Median (range)	9.43 (4.11–17.51)	25.00 (7.92–54.38)
Week 24, n	45	40
Mean ± SD	10.18 ± 3.95	25.15 ± 12.73
Median (range)	9.76 (5.29–24.83)	23.63 (6.79–67.26)
Final evaluation, n	52	44
Mean ± SD	10.76 ± 6.56	25.06 ± 12.22
Median (range)	9.73 (4.75–47.74)	23.74 (6.79–67.26)
Follow-up visit, n	51	44
Mean ± SD	12.90 ± 7.07	12.61 ± 6.28
Median (range)	10.21 (5.38–41.58)	11.25 (3.27–26.78)

SD, standard deviation

Supplementary figure 1 Diagnosis flow of CCA

Supplementary figure 2 Subgroup analysis with various background factors in pooled patient group, KPS1301 Subgroup (excluding 1.6 mg) and KPS1305 (excluding patient who had previously participated in a rovatirelin clinical study)



I² is measure of heterogeneity across the studies, ranging from 0–100%. A value of 0% indicates no heterogeneity, and larger values show increasing heterogeneity.

P-value of Interaction is an interaction test used for assessing the heterogeneity of the between-group difference across subgroups within the same factor.