

Supplementary file submitted to CNS Drugs

**Multiple Adverse Outcomes Associated with Risperidone in People with
Dementia: An Individual Participant Data Meta-Analysis**

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Table S1. Trial characteristics

	AUS-5	BEL-14	INT-24	USA-063	INT-83	USA-232
ClinicalTrials.gov identifier (NCT number)	NCT00249158	N/A	NCT00249145	NCT00253123	N/A	NCT00034762
Trial design	Double-blind, Placebo- controlled Parallel-group trial	Double-blind, placebo- controlled trial	Placebo-controlled, Double-blind, Parallel- group trial	Double-Blind, Placebo- Controlled trial	A double-blind, placebo- controlled, parallel-group trial	Double-blind, Placebo- controlled Parallel-group trial
Duration of trials	12 weeks	4 weeks	12 weeks	12 weeks	8 weeks	8 weeks
Location	Australia and New Zealand	Belgium	8 countries	USA	USA, the U.K., Poland, Austria, Israel	USA
Number of participants at baseline						
Total	337	39	344	625	18	473
Placebo	170	19	114	163	8	238
Risperidone	167	20	115	462	10	235
Haloperidol	0	0	115	0	0	0
Inclusion criteria						
Age	>55	>65	>55	>55	>55	>55
Dementia diagnosis	Alzheimer's, vascular, or mixed dementia based on DSM-IV criteria, and with behavioural disturbances	Diagnosis of Senile Dementia of the Alzheimer Type (criteria of Berg et al) Staging of dementia of 1, 2 or 3 on the Clinical Dementia Rating scale.	Alzheimer's, vascular, or mixed dementia based on DSM-IV criteria, and with behavioural disturbances	Alzheimer's, vascular, or mixed dementia based on DSM-IV criteria, and with behavioural disturbances	Alzheimer's, vascular, or mixed dementia based on DSM-IV criteria, and with behavioural disturbances	Alzheimer's, vascular, or mixed dementia based on DSM-IV criteria, and with behavioural disturbances

Functional Assessment Staging Tool (FAST) score for Alzheimer's Disease	4 or more	-	4 or more	4 or more	-	-
Mini-Mental State Examination (MMSE) score	23 or lower	-	23 or lower	23 or lower	5 to 23	5 to 23
Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) total scores	-	-	8 or more	8 or more	-	-
Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) subscale scores	2 or more on any subscale	-	-	-	2 or more on any subscale	2 or more on any subscale
Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) global rating	-	-	1 or more	1 or more	-	-
Cohen-Mansfield Agitation Inventory (CMAI) frequency score on aggressive items	Yes	-	-	-	-	-
Residents of an aged care facility	Yes	Yes	Yes	Yes	Yes	Yes
Exclusion criteria						
Neurological/Psychiatric conditions						
Medical/neurological conditions* other than dementia which diminish cognitive function	Yes	Yes	Yes	Yes	Yes	Yes

Other psychiatric disorders (major depression within the last 6 months, bipolar affective disorder, schizophrenia or schizoaffective disorder, delirium, etc)	Yes	Yes	Yes	Yes	Yes	Yes
Known by other causes of dementia (pure vascular dementia, human immunodeficiency virus) or reversible causes of dementia	No	Yes	No	Yes	Yes	Yes
Other medical conditions						
Clinically relevant or history of tardive dyskinesia	Yes	-	No	No	No	No
Clinically uncontrolled medical conditions	Yes	-	No	Yes	Yes	Yes
Clinically significant laboratory or electrocardiogram (ECG) findings.	Yes	-	Yes	Yes	Yes	Yes
Hypersensitivity or Immune mediated reaction to antipsychotics/risperidone or history of Neuroleptic Malignant Syndrome (NMS)	Yes	-	Yes	Yes	Yes	Yes
Seizure disorder requiring medication	Yes	-	No	Yes	Yes	Yes
Female subjects of childbearing potential without adequate contraception	No	-	No	Yes	No	Yes
Carcinoma in the past five years/Malignant melanoma	No	-	No	Yes	No	Yes
Medication use						
Substance-induced dementia (alcohol, etc.); Psychoactive Substance (including alcohol) Abuse or Dependence	Yes	-	Yes	Yes	Yes	Yes

History use of depot injection antipsychotics within 1 or 2 treatment cycle	Within 2 treatment cycles	-	Within 1 treatment cycle	Within 1 treatment cycle	Within 1 treatment cycle	Within 1 treatment cycle
Participants of other trials within 4 weeks	Yes	-	Yes	Yes	Yes	Yes
Received concomitant medications for chronic conditions for less than 30 days (expect OTC drugs and antibiotics)	No	-	No	Yes	Yes †	Yes
Expected to continue treatment with antipsychotics, antidepressants, lithium, carbamazepine, trazodone and/or valproic acid or other anticonvulsants during the trial.	No	-	No	Yes	Yes	Yes
History or risk of engaging in behaviour that could harm themselves or others.	No	-	No	Yes	Yes	Yes
Intervention						
Dose	A flexible dose from 0.5 mg to 2 mg/day	A flexible dose from 1 mg to 4 mg/day	A flexible dose from 0.5 mg to 4 mg/day	A fixed-dose regimens of 0.5 mg, 1 mg, or 2 mg/day	A flexible dose from 1 mg to 1.5 mg/day	A flexible dose from 1 mg to 1.5 mg/day
Non-pharmacological measures	Not available	Not available	Not available	Not available	Not available	Not available
Efficacy assessment						
Cohen-Mansfield Agitation Inventory (CMAI)	Yes	-	Yes	Yes	-	-
Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) rating scale	Yes	Yes	Yes	Yes	Yes	Yes

*Including, but not limited to: drug overdose, severe liver, kidney, lung or heart dysfunction, severe anaemia, untreated hypothyroidism, vitamin B12 or folic acid deficiency, uncontrolled diabetes, Parkinson's disease, Huntington's disease, Huntington's chorea, progressive supranuclear paralysis, toxic confusional state, brain tumor,

subdural hematoma, multiple sclerosis, brain trauma, Creutzfeldt-Jakob disease, Lewy Body dementia, and other conditions such as electrolyte imbalance, sepsis syndrome, and mental retardation.

† And those receiving Cognex® or Hydergine® and are not willing to discontinue use during the study period.

Abbreviation: BEHAVE-AD, Behavioural Pathology in Alzheimer's Disease Rating Scale; CMAI, Cohen-Mansfield Agitation Inventory; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; ECG, Electrocardiogram; FAST, Functional Assessment Staging Tool score for Alzheimer's Disease; MMSE, Mini-Mental State Examination; NSM, Neuroleptic Malignant Syndrome; OTC, Over the counter

Table S2. Extraction of adverse outcomes in all trials

Grouped outcome (for analysis)	Original group of adverse events (as reported in trial)	Original adverse event (as reported in trial)
Cerebrovascular adverse events (CVAE)	Vascular (extracardiac) disorders	Cerebrovascular disorder
	Vascular (extracardiac) disorders	Cerebral haemorrhage
	Vascular (extracardiac) disorders	Haemorrhage intracranial
5-point Major Adverse Cardiovascular Events (MACE)	Cardiovascular disorders, general	Cardiac failure
	Cardiovascular disorders, general	Cardiac failure left
	Vascular (extracardiac) disorders	Cerebrovascular disorder
	Vascular (extracardiac) disorders	Cerebral haemorrhage
	Heart rate and rhythm disorders	Cardiac arrest
	Myo endo pericardial & valve disorders	Myocardial infarction
	Death	Cardiovascular death
Pneumonia	Respiratory system disorders	Pneumonia
	Respiratory system disorders	Pneumonia lobar
Falls	Body as a whole - general disorders	Fall
Somnolence	Psychiatric disorders	Somnolence
Extrapyramidal symptoms	Central and Peripheral Nervous System Disorders	Dyskinesia
	Central and Peripheral Nervous System Disorders	Dyskinesia tardive
	Central and Peripheral Nervous System Disorders	Dystonia
	Central and Peripheral Nervous System Disorders	Extrapyramidal disorder
	Central and Peripheral Nervous System Disorders	Gait abnormal
	Central and Peripheral Nervous System Disorders	Muscle contractions involuntary
	Central and Peripheral Nervous System Disorders	Parkinsonism aggravated
	Central and Peripheral Nervous System Disorders	Tremor
	Central and Peripheral Nervous System Disorders	Hypertonia
	Central and Peripheral Nervous System Disorders	Hypokinesia
Upper respiratory tract infection	Respiratory system disorders	Upper resp tract infection
	Respiratory system disorders	Rhinitis

Abbreviations: CVAE, cerebrovascular adverse events; MACE, major adverse cardiovascular event

Table S3. Variable description

Variables	Unit	Description	Types
Trial	USA-5; BEL-14; INT-24; INT-83; USA-063; USA-232	Name of trials	Categorical
Age	Years		Continuous
Sex	Male/Female		Categorical
BMI	Weight/Height ²	Body mass index (BMI)	Continuous
MMSE	-	Mini-mental state examination (MMSE) score	Continuous
Demetia diagnosis	Alzheimer's disease Vascular dementia Mixed type dementia		Categorical
BEHAVE-AD total score at baseline	-	The sum of all BEHAVE-AD subscale score	Continuous
Presence of psychosis symptom at baseline	Yes/No	Score ≥ 2 on any items in the BEHAVE-AD subscales A and B	Categorical
Presence of activity disturbances symptom at baseline	Yes/No	score ≥ 1 on any items in the BEHAVE-AD subscale C	Categorical
Presence of aggression symptom at baseline	Yes/No	score ≥ 1 on any items in the BEHAVE-AD subscale D	Categorical
Presence of sleep symptom at baseline	Yes/No	score ≥ 1 on any items in the BEHAVE-AD subscale E	Categorical
Presence of affective disturbances symptom at baseline	Yes/No	score ≥ 1 on any items in the BEHAVE-AD subscale F	Categorical
Presence of anxieties and phobias symptom at baseline	Yes/No	score ≥ 1 on any items in the BEHAVE-AD subscale G	Categorical
Any use of cardiovascular drugs at baseline	Yes/No	This category includes all drugs with ATC code B01, C02, C03, C07, C08, C09.	Categorical
Any use of diuretics drugs at baseline	Yes/No	This category includes all drugs with ATC code C03	Categorical
Any use of antidiabetic drugs at baseline	Yes/No	This category includes all drugs with ATC code A10	Categorical
Any use of musculo-skeletal drugs at baseline	Yes/No	This category includes all drugs with ATC code M	Categorical
Any use of psychotropic drugs at baseline	Yes/No	This category includes all drugs with ATC code N02A, N03, N05, N06A. Prochlorperazine (ATC N05AB04) was excluded from this category	Categorical

Any use of opioids at baseline	Yes/No	This category includes all drugs with ATC code N02A and codein (ATC R05DA04)	Categorical
Any use of antiepileptics at baseline	Yes/No	This category includes all drugs with ATC code N03	Categorical
Any use of antidepressants at baseline	Yes/No	This category includes all drugs with ATC code N06A	Categorical
Any use of antipsychotics at baseline	Yes/No	This category includes all drugs with ATC code N05A, except Prochlorperazine (ATC N05AB04)	Categorical
Any use of sedatives, hypnotics, and anxiolytics drugs at baseline	Yes/No	This category includes all drugs with ATC code N05B and N05C	Categorical
Any use of sedatives, hypnotics, and anxiolytics drugs during trials	Yes/No	This category includes all drugs with ATC code N05B and N05C	Categorical
Any use of opioids during trials	Yes/No	This category includes all drugs with ATC code N02A and codeine (ATC R05DA04)	Categorical

Abbreviations: ATC, Anatomical Therapeutic Chemical; BEHAVE-AD, Behavioural Pathology in Alzheimer's Disease; BMI, body mass index; MMSE, Mini-Mental State Examination

Table S4. Benjamini–Hochberg (B-H) corrections for multiple adverse outcomes associated with risperidone use

Model	p-value	Index	B-H critical	Significant
Short-term upper respiratory tract infections	0.949186	1	0.025	
Pneumonia	0.671153	2	0.023529	
Falls	0.659066	3	0.022059	
Serum sodium concentration	0.464305	4	0.020588	
All-cause mortality	0.426399	5	0.019118	
Fasting blood glucose	0.125082	6	0.017647	
Short-term extrapyramidal symptoms	0.022899	7	0.016176	
Long-term upper respiratory tract infections	0.008563	8	0.014706	*
Mini-Mental State Examination score	0.007761	9	0.013235	*
Major adverse cardiovascular events	0.005509	10	0.011765	*
Cerebrovascular adverse events	0.000985	11	0.010294	*
Body weight at endpoint	0.000966	12	0.008824	*
Long-term extrapyramidal symptoms	0.000137	13	0.007353	*
Long-term somnolence	0.000114	14	0.005882	*
Parkinsonism (ESRS subscale score)	6.31E-05	15	0.004412	*
Short-term somnolence	3.9E-05	16	0.002941	*
Parkinsonism (Simpson–Angus Scale score)	3.95E-06	17	0.001471	*

*Statistically significant

Abbreviation: B-H, Benjamini-Hochberg; ESRS, Extrapyramidal Symptom Rating Scale

Table S5. Predictors of CVAEs, fall and pneumonia in the risperidone and placebo group.

Predictors	CVAE model				Fall model				Pneumonia model			
	Risperidone (N=843)		Placebo (N=625)		Risperidone (N=843)		Placebo (N=625)		Risperidone (N=843)		Placebo (N=625)	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age (years)	1.02 (0.96 to 1.08)	0.552	1.12 (0.98 to 1.28)	0.1043	1.01 (0.99 to 1.03)	0.4721	1.04 (1.01 to 1.07)	0.0042	1.03 (0.98 to 1.09)	0.2139	1.07 (1.01 to 1.14)	0.0256
Sex (Reference: Female)												
Male	1.25 (0.54 to 2.89)	0.6074	2.09 (0.37 to 11.75)	0.4007	1.46 (1.02 to 2.11)	0.0411	1.23 (0.8 to 1.89)	0.3464	2.38 (1.11 to 5.09)	0.0254	1.28 (0.47 to 3.5)	0.6358
BMI (kg/m²)	0.95 (0.87 to 1.04)	0.289	0.88 (0.7 to 1.09)	0.2264	0.99 (0.95 to 1.02)	0.4666	0.98 (0.93 to 1.02)	0.3137	0.92 (0.84 to 1)	0.0557	1.01 (0.91 to 1.11)	0.878
MMSE score	1 (0.94 to 1.07)	0.9975	1.14 (0.99 to 1.31)	0.0603	0.98 (0.95 to 1.01)	0.1319	0.98 (0.95 to 1.02)	0.282	1 (0.94 to 1.06)	0.9929	0.91 (0.83 to 0.98)	0.0199
Dementia type (Reference: Alzheimer's disease)												
Mixed type dementia	1.49 (0.46 to 4.8)	0.5069	-	-	1.22 (0.68 to 2.18)	0.5096	1.25 (0.61 to 2.58)	0.5387	1.52 (0.5 to 4.57)	0.4605	1.27 (0.27 to 5.85)	0.7621
Vascular dementia	1.11 (0.44 to 2.83)	0.8213	-	-	1.41 (0.94 to 2.12)	0.0953	1.95 (1.23 to 3.08)	0.0042	1.16 (0.48 to 2.79)	0.7432	0.78 (0.25 to 2.46)	0.6756
Presence of BPSD at baseline												
Psychosis	0.32 (0.12 to 0.85)	0.0224	0.31 (0.04 to 2.3)	0.2506	1.48 (0.96 to 2.26)	0.0732	0.83 (0.5 to 1.38)	0.4726	0.73 (0.31 to 1.74)	0.4812	1.01 (0.34 to 2.99)	0.9836
Activity disturbances	0.53 (0.2 to 1.35)	0.1829	0.35 (0.05 to 2.51)	0.2988	1.02 (0.6 to 1.74)	0.9276	4.69 (1.83 to 12.06)	0.0013	1.17 (0.39 to 3.54)	0.7788	2.22 (0.47 to 10.56)	0.3173
Aggressiveness	0.97 (0.2 to 4.66)	0.9666			1.58 (0.8 to 3.15)	0.1899	0.69 (0.31 to 1.51)	0.3473	1.54 (0.33 to 7.2)	0.5811	1.15 (0.14 to 9.67)	0.8999
Affective disturbances	1.94 (0.86 to 4.38)	0.1109	0.51 (0.09 to 2.91)	0.4448	0.96 (0.68 to 1.37)	0.8312	0.96 (0.63 to 1.48)	0.8581	0.79 (0.36 to 1.73)	0.5534	1.12 (0.43 to 2.89)	0.8184

Sleep disturbances	0.55 (0.24 to 1.29)	0.170 6	4.05 (0.68 to 24.01)	0.123 7	1.13 (0.8 to 1.6)	0.495 3	1.19 (0.79 to 1.79)	0.417 4	0.8 (0.36 to 1.77)	0.575 6	0.86 (0.35 to 2.15)	0.753 9
Anxieties/Phobias	1.46 (0.59 to 3.63)	0.409 4	1.53 (0.21 to 10.95)	0.673 3	1.36 (0.93 to 1.98)	0.112	0.61 (0.4 to 0.95)	0.026 9	1.23 (0.56 to 2.67)	0.605 5	0.59 (0.23 to 1.53)	0.277 1
Total BEHAVE-AD score at baseline	1.12 (0.65 to 1.95)	0.680 2	0.93 (0.29 to 2.92)	0.896 9	0.99 (0.79 to 1.25)	0.945 8	1.13 (0.89 to 1.44)	0.303 2	0.83 (0.45 to 1.53)	0.546 5	1.12 (0.67 to 1.87)	0.678 1
Medication use at baseline												
Cardiovascular drugs	1.15 (0.51 to 2.6)	0.733	1.84 (0.36 to 9.31)	0.462 4	0.72 (0.51 to 1.02)	0.066 4	1.12 (0.74 to 1.7)	0.588 3	1.09 (0.51 to 2.33)	0.831 3	1.13 (0.47 to 2.73)	0.780 2
Cardiac therapy	2.14 (0.9 to 5.08)	0.084 1	1.15 (0.21 to 6.47)	0.870 8	1.33 (0.87 to 2.03)	0.182 8	1.32 (0.84 to 2.07)	0.235 4	1.83 (0.81 to 4.17)	0.148	1.03 (0.38 to 2.77)	0.951 9
Antidiabetic drugs	0.38 (0.05 to 2.96)	0.353 1			0.93 (0.52 to 1.66)	0.8	1.35 (0.63 to 2.89)	0.447 9	1.38 (0.46 to 4.18)	0.567 6	4.41 (1.34 to 14.55)	0.014 8
Musculo-skeletal drugs	2.56 (0.69 to 9.56)	0.161 5			1.77 (1.01 to 3.09)	0.045 1	0.34 (0.14 to 0.83)	0.018 8	1.78 (0.51 to 6.27)	0.366 5	1.08 (0.3 to 3.85)	0.905 1
Psychotropic drugs	0.46 (0.2 to 1.09)	0.076 7	1.93 (0.41 to 9.1)	0.405 5	1.09 (0.77 to 1.55)	0.625 4	1.27 (0.84 to 1.91)	0.253 4	0.67 (0.28 to 1.59)	0.367 1	2.2 (0.93 to 5.19)	0.072 3

Abbreviations: BMI, body mass index; BPSD, behaviours and psychological symptoms of dementia; CI, confidence interval; CVAE, cerebrovascular adverse events; HR, hazard ratio; MMSE, Mini-Mental State Examination.

Table S6. Predictors of somnolence before and after 4 weeks in the risperidone and placebo group

	Somnolence before week 4				Somnolence after week 4			
	Risperidone (N=833)		Placebo (N=622)		Risperidone (N=750)		Placebo (N=545)	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age (years)	1.06 (1.02 to 1.09)	0.0006	1.07 (1.02 to 1.13)	0.0091	1.02 (0.98 to 1.06)	0.2651	1.06 (1 to 1.12)	0.0697
Sex (Reference: Female)								
Male	0.98 (0.59 to 1.62)	0.9373	1.16 (0.52 to 2.61)	0.7132	1.3 (0.76 to 2.24)	0.3401	2.16 (0.84 to 5.55)	0.1098
BMI (kg/m2)	1.02 (0.97 to 1.07)	0.5073	1.01 (0.93 to 1.09)	0.8322	1.02 (0.97 to 1.08)	0.4642	0.97 (0.88 to 1.07)	0.5975
MMSE score	0.97 (0.94 to 1.01)	0.1446	0.98 (0.92 to 1.05)	0.5757	0.98 (0.94 to 1.03)	0.4149	0.96 (0.89 to 1.04)	0.3517
Dementia type (Reference: Alzheimer's disease)								
Mixed type dementia	1.33 (0.63 to 2.81)	0.4544	1.39 (0.41 to 4.69)	0.5999	1.81 (0.83 to 3.91)	0.1337	1.48 (0.35 to 6.24)	0.593
Vascular dementia	1.1 (0.62 to 1.94)	0.7567	1.52 (0.65 to 3.55)	0.3369	1.02 (0.53 to 1.95)	0.9638	1.39 (0.5 to 3.84)	0.5278
Presence of BPSD at baseline								
Psychosis	1.2 (0.69 to 2.1)	0.517	2.39 (0.88 to 6.5)	0.0876	0.84 (0.46 to 1.56)	0.5857	0.69 (0.22 to 2.16)	0.5191
Activity disturbances	0.82 (0.44 to 1.53)	0.5339	2.54 (0.74 to 8.81)	0.1403	1.14 (0.55 to 2.36)	0.7216	0.31 (0.09 to 1.05)	0.0598
Aggressiveness	0.96 (0.46 to 2.01)	0.9077	0.85 (0.17 to 4.25)	0.8477	0.79 (0.36 to 1.76)	0.5675	1 (0.12 to 8.72)	0.9978
Affective disturbances	0.96 (0.61 to 1.52)	0.8711	1.08 (0.5 to 2.34)	0.8486	0.85 (0.51 to 1.43)	0.5475	1.28 (0.49 to 3.31)	0.6147
Sleep disturbances	1.15 (0.73 to 1.8)	0.5496	1.62 (0.76 to 3.42)	0.2081	0.98 (0.58 to 1.65)	0.9457	1.15 (0.48 to 2.74)	0.7559
Anxieties/Phobias	1.09 (0.67 to 1.76)	0.7265	0.73 (0.31 to 1.69)	0.4588	1.25 (0.73 to 2.13)	0.4217	0.62 (0.23 to 1.68)	0.3493
Total BEHAVE-AD score at baseline	0.99 (0.72 to 1.35)	0.9342	0.83 (0.53 to 1.29)	0.4012	0.95 (0.66 to 1.36)	0.7633	1.81 (1.12 to 2.93)	0.0148
Medication use at baseline								
Cardiovascular drugs	0.65 (0.41 to 1.02)	0.0633	0.99 (0.46 to 2.16)	0.9894	0.77 (0.46 to 1.29)	0.3236	0.47 (0.19 to 1.15)	0.0972
Cardiac therapy	1.26 (0.72 to 2.21)	0.4122	0.59 (0.22 to 1.57)	0.2929	2.01 (1.11 to 3.65)	0.0208	1.13 (0.41 to 3.13)	0.8119
Antidiabetic drugs	0.93 (0.42 to 2.06)	0.8604	3.93 (1.22 to 12.69)	0.0219	1.23 (0.56 to 2.69)	0.6052	2.12 (0.5 to 8.98)	0.3096
Musculo-skeletal drugs	0.42 (0.15 to 1.22)	0.1122	0.71 (0.19 to 2.73)	0.6201	0.43 (0.13 to 1.45)	0.1725	1.52 (0.45 to 5.14)	0.4961
Psychotropic drugs	1.05 (0.65 to 1.68)	0.8537	1.36 (0.65 to 2.82)	0.4166	0.82 (0.47 to 1.44)	0.4971	0.72 (0.29 to 1.78)	0.475

Abbreviations: BMI, body mass index; BPSD, behaviours and psychological symptoms of dementia; CI, confidence interval; OR, Odds ratio; MMSE, Mini-Mental State Examination.

Table S7. Predictors of extrapyramidal symptoms before and after 4 weeks in the risperidone and placebo group.

	Extrapyramidal symptoms before week 4				Extrapyramidal symptoms after week 4			
	Risperidone (N=870)		Placebo (N=626)		Risperidone (N=757)		Placebo (N=549)	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age (years)	1.04 (1 to 1.08)	0.0437	1.01 (0.96 to 1.07)	0.6169	1.02 (0.98 to 1.06)	0.4412	0.95 (0.88 to 1.02)	0.1313
Sex (Reference: Female)								
Male	1.52 (0.86 to 2.69)	0.1528	1.51 (0.68 to 3.33)	0.3122	1.44 (0.79 to 2.65)	0.2343	1.95 (0.67 to 5.64)	0.219
BMI (kg/m²)	1.05 (0.99 to 1.11)	0.0809	1.04 (0.96 to 1.13)	0.3117	1.03 (0.97 to 1.1)	0.2992	1.15 (1.05 to 1.26)	0.0031
MMSE score	0.97 (0.92 to 1.01)	0.1187	0.98 (0.91 to 1.04)	0.4961	1.01 (0.96 to 1.06)	0.7249	0.98 (0.9 to 1.08)	0.7295
Dementia type (Reference: Alzheimer's disease)								
Mixed type dementia	1.58 (0.66 to 3.74)	0.3028	2.24 (0.67 to 7.55)	0.1928	2.64 (1.21 to 5.77)	0.0151	0.55 (0.06 to 5.18)	0.5997
Vascular dementia	1.43 (0.75 to 2.75)	0.2813	2.17 (0.9 to 5.25)	0.0856	1.05 (0.5 to 2.21)	0.9048	0.67 (0.17 to 2.69)	0.5729
Presence of BPSD at baseline								
Psychosis	0.9 (0.46 to 1.75)	0.7562	0.59 (0.22 to 1.63)	0.3113	0.76 (0.38 to 1.54)	0.4445	0.3 (0.08 to 1.13)	0.0756
Activity disturbances	0.62 (0.3 to 1.31)	0.2108	2.6 (0.55 to 12.25)	0.2283	1.21 (0.51 to 2.9)	0.6639		0.995
Aggressiveness	0.92 (0.35 to 2.39)	0.8575	0.42 (0.1 to 1.72)	0.225	0.63 (0.25 to 1.61)	0.3374	0.94 (0.13 to 6.83)	0.9493
Affective disturbances	0.91 (0.51 to 1.6)	0.7393	0.9 (0.39 to 2.08)	0.8083	0.88 (0.49 to 1.58)	0.6564	3.76 (1.16 to 12.26)	0.0278
Sleep disturbances	0.97 (0.56 to 1.7)	0.9286	0.87 (0.39 to 1.94)	0.7314	1.31 (0.74 to 2.32)	0.3553	0.75 (0.24 to 2.35)	0.6272
Anxieties/Phobias	1.29 (0.71 to 2.35)	0.4063	0.69 (0.29 to 1.64)	0.3996	1.25 (0.67 to 2.34)	0.4767	1.86 (0.48 to 7.19)	0.3668
Total BEHAVE-AD score at baseline	1.2 (0.83 to 1.75)	0.3365	1.38 (0.87 to 2.19)	0.1715	1.16 (0.79 to 1.7)	0.4393	0.98 (0.51 to 1.88)	0.9406
Medication use at baseline								
Cardiovascular drugs	0.91 (0.52 to 1.57)	0.7297	1.49 (0.66 to 3.39)	0.3367	0.69 (0.39 to 1.23)	0.2122	0.45 (0.14 to 1.44)	0.1806
Cardiac therapy	0.92 (0.45 to 1.88)	0.8143	0.68 (0.24 to 1.91)	0.4608	1.22 (0.59 to 2.54)	0.5951	0.83 (0.2 to 3.39)	0.7977
Antidiabetic drugs	0.97 (0.39 to 2.42)	0.9539	0.56 (0.07 to 4.47)	0.5825	0.45 (0.13 to 1.5)	0.1926	1.08 (0.12 to 9.92)	0.9457
Musculo-skeletal drugs	0.35 (0.08 to 1.51)	0.1599	0.95 (0.26 to 3.46)	0.943	0.69 (0.2 to 2.38)	0.5557	1.39 (0.28 to 6.88)	0.6878
Psychotropic drugs	1.38 (0.81 to 2.35)	0.2356	1.07 (0.47 to 2.45)	0.8741	1.24 (0.68 to 2.25)	0.4854	2.28 (0.8 to 6.52)	0.1225

Abbreviations: BMI, body mass index; BPSD, behaviours and psychological symptoms of dementia; CI, confidence interval; OR, Odds ratio; MMSE, Mini-Mental State Examination.

Table S8. Predictors of Upper respiratory tract infections before and after 4 weeks in the risperidone and placebo group.

	Upper respiratory tract infections before week 4				Upper respiratory tract infections after week 4			
	Risperidone (N=877)		Placebo (N=623)		Risperidone (N=753)		Placebo (N=546)	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age (years)	1.02 (0.97 to 1.07)	0.4916	1.04 (0.98 to 1.1)	0.1822	1 (0.95 to 1.04)	0.9284	1.04 (0.96 to 1.13)	0.3759
Sex (Reference: Female)								
Male	1.59 (0.73 to 3.46)	0.2423	0.97 (0.38 to 2.47)	0.9509	1.33 (0.67 to 2.67)	0.4164	0.77 (0.21 to 2.87)	0.7023
BMI (kg/m²)	1.02 (0.95 to 1.1)	0.5941	0.96 (0.87 to 1.06)	0.3893	0.99 (0.92 to 1.06)	0.6909	1.06 (0.95 to 1.17)	0.3015
MMSE score	1.01 (0.95 to 1.07)	0.7822	1.02 (0.95 to 1.09)	0.5446	0.97 (0.92 to 1.03)	0.3482	1.03 (0.94 to 1.13)	0.5318
Dementia type (Reference: Alzheimer's disease)								
Mixed type dementia	1 (0.28 to 3.54)	0.996	1.17 (0.24 to 5.62)	0.8438	1.26 (0.45 to 3.52)	0.653	0.75 (0.08 to 6.75)	0.7997
Vascular dementia	1.04 (0.43 to 2.53)	0.9244	1.78 (0.67 to 4.71)	0.248	1.07 (0.47 to 2.45)	0.8657	1.09 (0.26 to 4.47)	0.9084
Presence of BPSD at baseline								
Psychosis	0.52 (0.22 to 1.25)	0.1464	0.45 (0.16 to 1.25)	0.1257	0.52 (0.24 to 1.12)	0.0947	0.29 (0.07 to 1.16)	0.0802
Activity disturbances	0.9 (0.32 to 2.58)	0.8515	1.73 (0.44 to 6.85)	0.4332	0.78 (0.32 to 1.94)	0.5958	2.41 (0.24 to 24.48)	0.4571
Aggressiveness	2.07 (0.45 to 9.59)	0.3529	2.67 (0.32 to 22.55)	0.3679	2.31 (0.51 to 10.44)	0.2757	0.43 (0.07 to 2.57)	0.3519
Affective disturbances	2.61 (1.24 to 5.49)	0.0116	0.52 (0.2 to 1.33)	0.1742	1.95 (1.02 to 3.75)	0.0449	1.11 (0.33 to 3.65)	0.8694
Sleep disturbances	1.12 (0.54 to 2.34)	0.7549	1.24 (0.5 to 3.05)	0.6388	1.58 (0.82 to 3.02)	0.1718	1.03 (0.33 to 3.22)	0.9549
Anxieties/Phobias	1.15 (0.52 to 2.56)	0.7345	1.09 (0.42 to 2.85)	0.8549	1.03 (0.52 to 2.06)	0.9259	1.53 (0.36 to 6.46)	0.5647
Total BEHAVE-AD score at baseline	1.11 (0.67 to 1.84)	0.6801	0.8 (0.42 to 1.54)	0.5115	1.06 (0.68 to 1.66)	0.7959	1.27 (0.65 to 2.49)	0.4784
Medication use at baseline								
Cardiovascular drugs	1.13 (0.55 to 2.36)	0.7365	1.22 (0.51 to 2.89)	0.6573	0.7 (0.36 to 1.37)	0.3009	0.13 (0.03 to 0.63)	0.0116
Cardiac therapy	1.86 (0.84 to 4.1)	0.1248	0.65 (0.21 to 2.03)	0.4613	0.75 (0.29 to 1.9)	0.5391	0.81 (0.16 to 4.12)	0.7973
Antidiabetic drugs	0.92 (0.26 to 3.25)	0.8997	2.19 (0.56 to 8.54)	0.2593	1.07 (0.36 to 3.23)	0.9001	1.22 (0.12 to 12.89)	0.868
Musculo-skeletal drugs	0.31 (0.04 to 2.36)	0.2559	-	-	1.28 (0.36 to 4.57)	0.7012	-	-
Psychotropic drugs	0.36 (0.15 to 0.9)	0.0296	0.71 (0.29 to 1.72)	0.4438	0.67 (0.3 to 1.52)	0.3356	3.31 (1.1 to 9.91)	0.0325

Abbreviations: BMI, body mass index; BPSD, behaviours and psychological symptoms of dementia; CI, confidence interval; OR, Odds ratio; MMSE, Mini-Mental State Examination.

Table S9. Predictors of cognitive function and weight changes in the risperidone and placebo group

	MMSE changes from baseline				Weight changes from baseline			
	Risperidone (N=753)		Placebo (N=546)		Risperidone (N=782)		Placebo (N=546)	
	MD (95% CI)	p	MD (95% CI)	p	MD (95% CI)	p	MD (95% CI)	p
Age (years)	0.02 (-0.03 to 0.06)	0.4262	0 (-0.05 to 0.05)	0.9513	0.01 (-0.02 to 0.05)	0.4175	0 (-0.03 to 0.04)	0.8805
Sex (Reference: Female)								
Male	-0.03 (-0.74 to 0.68)	0.9391	-0.72 (-1.52 to 0.09)	0.0827	-0.53 (-1.06 to 0)	0.0485	0.11 (-0.47 to 0.7)	0.704
BMI (kg/m²)	0 (-0.07 to 0.08)	0.9044	0.02 (-0.06 to 0.11)	0.6019	-0.08 (-0.13 to -0.03)	0.002	-0.09 (-0.15 to -0.03)	0.0015
MMSE score	-	-	-	-	-0.01 (-0.05 to 0.03)	0.691	0.05 (0 to 0.09)	0.0505
Dementia type (Reference: Alzheimer's disease)								
Mixed type dementia	-0.19 (-1.19 to 0.81)	0.7092	0.89 (-0.28 to 2.06)	0.1352	0.15 (-0.73 to 1.03)	0.7357	0.54 (-0.55 to 1.62)	0.3336
Vascular dementia	-0.34 (-1.16 to 0.48)	0.4154	0.22 (-0.68 to 1.12)	0.6267	0.12 (-0.52 to 0.77)	0.7106	0.26 (-0.44 to 0.95)	0.4652
Presence of BPSD at baseline								
Psychosis	-0.16 (-0.89 to 0.57)	0.6709	-0.03 (-0.89 to 0.83)	0.9392	-0.04 (-0.64 to 0.55)	0.8917	0.29 (-0.41 to 0.99)	0.4123
Activity disturbances	0.86 (-0.15 to 1.88)	0.0957	-0.55 (-1.82 to 0.73)	0.3983	-0.06 (-0.76 to 0.64)	0.8656	-0.02 (-0.87 to 0.83)	0.9573
Aggressiveness	0.54 (-0.65 to 1.73)	0.3751	0.33 (-1.51 to 2.16)	0.7259	-0.61 (-1.37 to 0.15)	0.1144	-0.02 (-0.98 to 0.94)	0.9699
Affective disturbances	-0.21 (-0.85 to 0.44)	0.5293	-0.23 (-1.02 to 0.56)	0.5726	0.19 (-0.3 to 0.68)	0.4434	-0.38 (-0.96 to 0.21)	0.2057
Sleep disturbances	0.09 (-0.55 to 0.73)	0.79	0.32 (-0.43 to 1.06)	0.4012	-0.25 (-0.74 to 0.25)	0.3262	-0.27 (-0.83 to 0.29)	0.3437
Anxieties/Phobias	0.15 (-0.51 to 0.8)	0.6613	-0.24 (-1.09 to 0.6)	0.5719	0.34 (-0.18 to 0.85)	0.1971	0.31 (-0.3 to 0.91)	0.3222
Total BEHAVE-AD score at baseline	0.03 (-0.43 to 0.48)	0.8994	-0.02 (-0.52 to 0.47)	0.9258	0.26 (-0.08 to 0.61)	0.1389	-0.11 (-0.46 to 0.23)	0.5264
Medication use at baseline								
Cardiovascular drugs	0.46 (-0.18 to 1.11)	0.1604	0.44 (-0.32 to 1.2)	0.2597	-0.03 (-0.5 to 0.45)	0.9141	0.21 (-0.34 to 0.76)	0.4541
Cardiac therapy	0.15 (-0.67 to 0.97)	0.7208	-1.11 (-2.05 to -0.17)	0.021	-0.46 (-1.07 to 0.15)	0.1399	-0.36 (-1.02 to 0.29)	0.2786
Antidiabetic drugs	0.07 (-1.07 to 1.2)	0.9069	1.13 (-0.69 to 2.96)	0.2231	-0.25 (-1.05 to 0.56)	0.5461	0.03 (-0.96 to 1.01)	0.9588
Musculo-skeletal drugs	-0.52 (-1.93 to 0.89)	0.4681	-0.77 (-2.1 to 0.55)	0.2529	-0.65 (-1.47 to 0.17)	0.1224	-0.13 (-0.94 to 0.68)	0.7482
Psychotropic drugs	0.06 (-0.62 to 0.75)	0.8565	-0.32 (-1.08 to 0.43)	0.4016	-0.06 (-0.57 to 0.46)	0.831	-0.06 (-0.61 to 0.49)	0.8283

Abbreviations: BMI, body mass index; BPSD, behaviours and psychological symptoms of dementia; CI, confidence interval; MD, Mean difference; MMSE, Mini-Mental State Examination.

Table S10. Predictors of serum sodium level and fasting blood glucose changes from baseline in the risperidone and placebo group.

	Serum sodium level changes from baseline				Fasting blood glucose changes from baseline			
	Risperidone (N=861)		Placebo (N=608)		Risperidone (N=861)		Placebo (N=608)	
	MD (95% CI)	p	MD (95% CI)	p	MD (95% CI)	p	MD (95% CI)	p
Age (years)	0 (-0.03 to 0.03)	0.9948	0.03 (0 to 0.07)	0.0803	-0.01 (-0.03 to 0.01)	0.4374	-0.02 (-0.04 to 0.01)	0.1472
Sex (Reference: Female)								
Male	0.37 (-0.15 to 0.89)	0.1642	0.08 (-0.49 to 0.64)	0.785	-0.29 (-0.64 to 0.06)	0.1076	0.23 (-0.17 to 0.63)	0.2663
BMI (kg/m2)	-0.02 (-0.07 to 0.03)	0.5222	-0.02 (-0.08 to 0.03)	0.439	0 (-0.03 to 0.04)	0.9258	-0.02 (-0.05 to 0.02)	0.4316
MMSE score	0.01 (-0.03 to 0.05)	0.5277	0.01 (-0.04 to 0.05)	0.7131	0.02 (-0.01 to 0.04)	0.1859	0 (-0.03 to 0.03)	0.8947
Dementia type (Reference: Alzheimer's diseases)								
Mixed type dementia	-0.1 (-0.98 to 0.78)	0.8208	0.84 (-0.19 to 1.88)	0.1111	-0.15 (-0.74 to 0.45)	0.6291	0.69 (-0.04 to 1.42)	0.0647
Vascular dementia	0.31 (-0.32 to 0.94)	0.337	0.46 (-0.2 to 1.12)	0.1746	0.32 (-0.11 to 0.75)	0.1396	-0.36 (-0.82 to 0.11)	0.1372
Presence of BPSD at baseline								
Psychosis	-0.15 (-0.74 to 0.44)	0.6138	0.28 (-0.39 to 0.95)	0.4055	0.06 (-0.33 to 0.45)	0.7611	0.12 (-0.35 to 0.58)	0.6235
Activity disturbances	-0.74 (-1.44 to -0.05)	0.0365	-0.2 (-1.03 to 0.63)	0.6378	-0.24 (-0.71 to 0.23)	0.3238	-0.09 (-0.67 to 0.49)	0.7656
Aggressiveness	-0.26 (-1.03 to 0.51)	0.5082	-0.03 (-0.99 to 0.94)	0.9538	-0.17 (-0.69 to 0.35)	0.5268	0.87 (0.18 to 1.55)	0.0133
Affective disturbances	0.13 (-0.37 to 0.62)	0.6158	-0.24 (-0.81 to 0.33)	0.4054	-0.06 (-0.39 to 0.28)	0.7455	-0.14 (-0.54 to 0.26)	0.5006
Sleep disturbances	0.21 (-0.28 to 0.7)	0.3992	-0.1 (-0.64 to 0.45)	0.7242	0.32 (-0.01 to 0.65)	0.0572	-0.01 (-0.4 to 0.38)	0.9596
Anxieties/Phobias	0.16 (-0.36 to 0.67)	0.5501	0.51 (-0.09 to 1.11)	0.0939	-0.04 (-0.39 to 0.31)	0.8243	0.2 (-0.22 to 0.63)	0.342
Total BEHAVE-AD score at baseline	0.07 (-0.28 to 0.41)	0.707	0 (-0.33 to 0.34)	0.9799	0 (-0.23 to 0.23)	0.9955	-0.09 (-0.32 to 0.15)	0.4744
Medication use at baseline								
Cardiovascular drugs	0.25 (-0.23 to 0.74)	0.3012	0.03 (-0.51 to 0.56)	0.9149	-0.07 (-0.4 to 0.26)	0.6776	-0.07 (-0.44 to 0.31)	0.7231
Cardiac therapy	0.04 (-0.57 to 0.65)	0.9007	0.34 (-0.3 to 0.99)	0.2946	0.62 (0.2 to 1.03)	0.0034	0.34 (-0.12 to 0.79)	0.1481
Antidiabetic drugs	0.23 (-0.57 to 1.03)	0.5672	-0.63 (-1.6 to 0.34)	0.2019	-0.58 (-1.12 to -0.04)	0.0344	0.15 (-0.53 to 0.83)	0.6689
Musculo-skeletal drugs	-0.06 (-0.91 to 0.79)	0.8899	0.06 (-0.76 to 0.87)	0.8916	0.02 (-0.57 to 0.6)	0.9589	-0.51 (-1.08 to 0.07)	0.0851
Psychotropic drugs	-0.28 (-0.79 to 0.23)	0.2885	-0.43 (-0.95 to 0.1)	0.1117	0.05 (-0.28 to 0.38)	0.7516	0.21 (-0.16 to 0.58)	0.2616

Abbreviations: BMI, body mass index; BPSD, behaviours and psychological symptoms of dementia; CI, confidence interval; MD, Mean difference; MMSE, Mini-Mental State Examination.

Table S11. Predictors of parkinsonism score changes from baseline in in the risperidone and placebo group.

	Parkinsonism score (ESRS scale) changes from baseline				Parkinsonism score (SAS scale) changes from baseline			
	Risperidone (N=637)		Placebo (N=377)		Risperidone (N=231)		Placebo (N=234)	
	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p
Age (years)	0 (-0.01 to 0.01)	0.8942	0.01 (0 to 0.02)	0.0457	0.03 (0 to 0.05)	0.0157	0 (-0.01 to 0.02)	0.9268
Sex (Reference: Female)								
Male	0.08 (-0.1 to 0.27)	0.3859	0.1 (-0.09 to 0.3)	0.309	0.21 (-0.14 to 0.56)	0.2478	0.23 (-0.03 to 0.49)	0.0807
BMI (kg/m2)	0.01 (-0.01 to 0.03)	0.3357	0.01 (-0.01 to 0.03)	0.3361	0.01 (-0.02 to 0.04)	0.4538	-0.01 (-0.03 to 0.01)	0.3217
Dementia type (Reference: Alzheimer's disease)								
Mixed type dementia	-0.04 (-0.31 to 0.24)	0.786	-0.18 (-0.46 to 0.1)	0.2025				
Vascular dementia	0.07 (-0.15 to 0.29)	0.5184	-0.2 (-0.42 to 0.02)	0.0716	0.09 (-0.36 to 0.54)	0.6824	0.12 (-0.22 to 0.46)	0.4995
Presence of BPSD at baseline								
Psychosis	0.15 (-0.04 to 0.35)	0.1174	-0.02 (-0.23 to 0.19)	0.8738	-0.24 (-0.79 to 0.32)	0.4001	-0.32 (-0.77 to 0.13)	0.1631
Activity disturbances	-0.09 (-0.36 to 0.17)	0.4882	0.19 (-0.11 to 0.49)	0.217	0.01 (-0.36 to 0.39)	0.9513	0.02 (-0.32 to 0.36)	0.8973
Aggressiveness	0.27 (-0.05 to 0.6)	0.1007	-0.15 (-0.59 to 0.29)	0.4974	-0.03 (-0.41 to 0.34)	0.8595	-0.28 (-0.61 to 0.05)	0.1003
Affective disturbances	0.03 (-0.14 to 0.2)	0.7109	-0.09 (-0.28 to 0.1)	0.3529	-0.23 (-0.56 to 0.1)	0.1634	-0.03 (-0.29 to 0.23)	0.8444
Sleep disturbances	-0.04 (-0.21 to 0.13)	0.6339	-0.02 (-0.2 to 0.16)	0.8305	-0.34 (-0.68 to 0)	0.0507	-0.15 (-0.42 to 0.11)	0.2628
Anxieties/Phobias	-0.14 (-0.32 to 0.03)	0.1118	-0.15 (-0.35 to 0.05)	0.1522	0.36 (0 to 0.71)	0.0475	-0.33 (-0.6 to -0.06)	0.0155
Total BEHAVE-AD score at baseline	-0.06 (-0.18 to 0.06)	0.318	-0.02 (-0.14 to 0.1)	0.7783	0.13 (-0.08 to 0.35)	0.2282	0.2 (0.05 to 0.34)	0.0071
Medication use at baseline								
Cardiovascular drugs	-0.03 (-0.21 to 0.14)	0.6954	0.04 (-0.14 to 0.23)	0.6569	-0.09 (-0.39 to 0.21)	0.555	0.19 (-0.05 to 0.43)	0.1266
Cardiac therapy	0.04 (-0.17 to 0.26)	0.693	0.05 (-0.18 to 0.28)	0.6784	-0.02 (-0.41 to 0.38)	0.9314	-0.13 (-0.4 to 0.15)	0.3665
Antidiabetic drugs	-0.25 (-0.54 to 0.04)	0.0852	0.3 (-0.14 to 0.73)	0.1793	0.35 (-0.12 to 0.82)	0.1471	-0.04 (-0.37 to 0.28)	0.7976
Musculo-skeletal drugs	-0.05 (-0.43 to 0.33)	0.785	-0.08 (-0.4 to 0.25)	0.6472	0.17 (-0.21 to 0.56)	0.371	-0.43 (-0.73 to -0.14)	0.0045
Psychotropic drugs	-0.13 (-0.31 to 0.06)	0.1838	-0.05 (-0.23 to 0.14)	0.624	0 (-0.29 to 0.29)	0.9905	-0.21 (-0.43 to 0)	0.054

Abbreviations: BMI, body mass index; BPSD, behaviours and psychological symptoms of dementia; CI, confidence interval; MD, Mean difference; MMSE, Mini-Mental State Examination.