Supplementary Material

Pilot Randomized, Double-Blind, Placebo-Controlled Crossover Trial Evaluating the Feasibility of an Intranasal Oxytocin in Improving Social Cognition in Individuals Living with Alzheimer's Disease

Supplementary Table 1. Complete list of observations, procedures, and scheduled visits

	Screening/ Recruitment	T_0 Pre-single dose administration 1	T_1 Post single dose administration 1	Check-in phone call	T_2 one-week Follow-up 1	Check-in phone call	1 week wash out, followed by crossover to alternate treatment Phone check-in between days 10- 12 to monitor AE/safety	T_3 Pre-single dose administration 2	T_4 Post single dose administration 2	Check-in phone call	T_5 one-week Follow-up 2	Check-in phone call	Early Termination
Day	0	0	0	3-5	7-10	10-13		14-17	14-17	17-20	21-24	24-27	
Informed Consent	X												
Inclusion/Exclusion Criteria	X	X											
Demographics	X												
Medical history (including NPI)	X				X			X			X		
Diagnosis	X												
HAM-D	X												
Benton Facial Recognition Test	X												
Current medications/treatment	X	X			X			X			X		
Social Cognition Assessment Facial Speed and Recognition Task		X	X		X			X	X		X		
Reading the Mind in the Eyes Test		X	X		X			X	X		X		
Emotion Evaluation Test		X			X			X			X		
Emotion Discrimination Test		X			X			X			X		
Questionnaires <u>Caregiver</u> IBM, ZBI, IRI subscales, AES, SDS, HBA Functional and Sleep Questionnaires, WHO (Five) Well-Being Index and GDS-15		X			X			X			X		
<u>Participant</u> WHO (Five) Well-Being Index and GDS-15		X			X			X			X		
Dispensing Medication		X						X					
Medication Compliance (collecting medications)					X						X		X
Adverse Events		X	X	X	X	X		X	X	X	X	X	X

NPI, Neuropsychiatric Inventory; HAM-D, Hamilton Depression Rating Scale; IBM, Intimate Bond Measure; ZBI, Zarit Burden Interview; IRI, Interpersonal Reactivity Index; AES, Apathy Evaluation Scale; SDS, Socioemotional Dysfunction Scale; HBA, Healthy Brain Ageing; WHO, World Health Organization; GDS-15, 15-item Geriatric Depression Scale.

Supplementary Table 2. Baseline clinical and demographic characteristics for each participant randomized to the trial

	Participant 1	Participant 2	Participant 3	Participant 4	Mean ± S.D. (n = 4)
Age, y	69	79	72	69	72.3 ± 4.7
Sex (males/females)	Female	Female	Male	Male	-
Ethnicity	White	White	White	White	-
Education, y	14	10	11	15	12.5 ± 2.4
Predicted IQ	107	103	115	-	108.3 ± 6.1[a]
MMSE, /30	22	28	29	23	25.5 ± 3.5
Body Mass Index	27.2	24.2	28.7	29.8	24.5 ± 2.4
Benton Facial Recognition Test	49	53	51	45	49.5 ±3.4
Hamilton Rating Depression Scale	1	0	6	0	1.8 ± 2.9
Neuropsychiatric Inventory	13	13	11	20	14.3 ± 3.9
QT/QTc Interval, milliseconds	384/377	384/396	430/405	400/423	399.5 ± 21.7 / 400.3 ± 19.1
WHO (Five) Well-Being Index	12	22	20	19	18.3 ± 4.3
15-item Geriatric Depression Scale	1	2	2	2	1.8 ± 0.5

IQ, Intelligent Quotient; MMSE, Mini-Mental State Examination; QTc, corrected QT interval; WHO, World Health Organization.
[a]Mean ± S.D. (n = 3)

Supplementary Table 3. Individual participant pre-single dose administration, post-single dose administration, and one-week follow up social cognitive test scores following placebo and oxytocin treatment

		Placebo Nasal Spray			Oxytocin Nasal Spray		
Participant	Social cognition Test	Pre-single dose administration	Post-single dose administration	One-week Follow-Up	Pre-single dose administration	Post-single dose administration	One-week Follow-Up
1	RMET, total raw score (*z*-score)	29 (0.8)	30 (1.1)	30 (1.1)	28 (0.5)	31 (1.3)	31 (1.3)
	FSAR, total score	24	27	23	22	23	26
	FSAR, mean speed	7.5	7.8	7.3	8.3	9.5	8.4
	EET, total score	19	-	22	18	-	20
	EDT, total score	17	-	18	18	-	18
2	RMET, total raw score (*z*-score)	28 (0.5)	27 (0.2)	24 (-0.6)	28 (0.5)	29 (0.8)	26 (-0.1)
	FSAR, total score	11	25	26	23	20	26
	FSAR, mean speed	6.0	8.5	8.6	8.6	8.5	9.1
	EET, total score	19	-	15	21	-	14
	EDT, total score	18	-	15	17	-	15
3	RMET, total raw score (*z*-score)	26 (-0.1)	27 (0.2)	30 (1.1)	29 (0.8)	21 (-1.4)	27 (0.2)
	FSAR, total score	28	22	22	19	26	22
	FSAR, mean speed	8.1	7.7	6.9	8.2	8.1	6.7
	EET, total score	22	-	20	22	-	17
	EDT, total score	18	-	18	17	-	17
4	RMET, total raw score (*z*-score)	25 (-0.3)	21 (-1.4)	19 (-2.0)	25 (-0.3)	22 (-1.2)	24 (-0.6)
	FSAR, total score	11	14	15	18	11	19
	FSAR, mean speed	10.0	8.6	7.6	6.7	6.4	6.0
	EET, total score	11	-	10	11	-	11
	EDT, total score	13	-	13	11	-	9

RMET, Reading the Mind in the Eyes Test; FSAR, Facial Speed and Recognition Task; EET, Emotion Evaluation Test; EDT, Emotion Discrimination Test.

Supplementary Table 4. Individual participant questionnaire data before pre-single dose administration and after one-week follow up for placebo and oxytocin treatment groups

		Placebo Nasal Spray		Oxytocin Nasal Spray	
Participant	Questionnaire	Pre-single dose administration	One-week Follow-Up	Pre-single dose administration	One-week Follow-Up
1	AES	45	45	43	44
	GDS-15 (CR)	3	1	0	2
	GDS-15 (SR)	4	3	1	4
	HBA FAQ	90	83	86	0
	HBA SQ	24	15	11	15
	IBM	20	26	26	26
	IRI-EC	14	17	14	14
	IRI-PT	17	13	14	13
	NPI	17	40	13	21
	SDS	126	124	118	116
	WHO-5 (CR)	14	17	15	16
	WHO-5 (SR)	13	17	12	17
	ZBI	35	36	35	39
2	AES	26	20	20	16
	GDS-15 (CR)	2	2	5	1
	GDS-15 (SR)	2	2	1	3
	HBA FAQ	0	0	0	0
	HBA SQ	7	7	7	7
	IBM	20	24	21	21
	IRI-EC	23	26	23	26
	IRI-PT	11	5	12	12
	NPI	13	20	12	15
	SDS	95	99	99	88
	WHO-5 (CR)	13	15	7	16
	WHO-5 (SR)	22	20	22	25
	ZBI	43	40	45	37

	AES	19	15	16	9
	GDS-15 (CR)	0	0	0	0
	GDS-15 (SR)	1	1	2	0
	HBA FAQ	9	2	25	0
	HBA SQ	5	2	8	4
	IBM	49	47	51	60
3	IRI-EC	16	15	15	13
	IRI-PT	12	12	13	11
	NPI	4	0	11	15
	SDS	89	82	58	65
	WHO-5 (CR)	18	21	18	20
	WHO-5 (SR)	22	22	20	20
	ZBI	26	26	27	22
	AES	28	32	31	32
	GDS-15 (CR)	6	6	5	4
	GDS-15 (SR)	2	1	1	1
	HBA FAQ	75	17	4	2
	HBA SQ	13	10	5	8
	IBM	33	30	27	37
4	IRI-EC	17	14	15	16
	IRI-PT	15	16	14	17
	NPI	20	15	5	9
	SDS	117	113	127	113
	WHO-5 (CR)	13	11	11	11
	WHO-5 (SR)	19	18	19	18
	ZBI	56	62	57	55

AES, Apathy Evaluation Scale; GDS-15 (CR/SR), 15-item Geriatric Depression Scale (caregiver-rated or self-report); HBA FAQ, Healthy Brain Ageing Functional Assessment Questionnaire; HBA SQ, Healthy Brain Ageing Sleep Questionnaire; IBM, Intimate Bond Measure; IRI-EC/PT, Interpersonal Reactivity Index-Empathic Concern/Perspective-Taking subscales; NPI, Neuropsychiatric Inventory; SDS, Socioemotional Dysfunction Scale; WHO-5 (CR/SR), World Health Organization (Five) Well-Being Index (caregiver-rated or self-report); ZBI, Zarit Burden Interview.

Supplementary Table 5. Individual participant medication adherence following one-week twice daily repeated administration for placebo and oxytocin treatment

	Placebo Nasal Spray		Oxytocin Nasal Spray	
Participant	Doses prescribed (doses)	Doses administered (doses, %)	Doses Prescribed (doses)	Doses administered (doses, %)
1	15	14, 93.3 %	17	17, 100 %
2	15	15, 100 %	15	15, 100 %
3	15	14, 93.3 %	17	16, 94.1 %
4	15	14, 93.3 %	15	15, 100 %

Supplementary Table 6. Frequency of all reported participant medications

	All Participants (n = 4)
Donepezil	3
Verapamil	1
Irbesartan	1
Clopidogrel + Aspirin	1
Pravastatin	1
Omega-3 fatty acid supplement	4
Vitamin supplementation (incl. folate, Vitamin B12, Vitamin B3, Vitamin D, Vitamin C, Calcium)	4
Coconut Oil Dietary Supplement	1
Tumeric Dietary Supplement	1
Gingko Biloba Dietary Supplement	1
Sustagen® Dietary Supplement	1
Souvenaid® Dietary Supplement	1

Supplementary Table 7. Frequency of side effects reported

	Placebo Nasal Spray (n = 4)	Oxytocin Nasal Spray (n = 4)
Mania	0	0
Hypomania	0	0
Hyperkinesia	0	0
Movement disorder	0	0
GI upset (constipation, diarrhea, vomiting)	0	0
Hot flush (if applicable)	0	0
Malaise	0	0
Weight change	0	0
Seizure	0	0
Teeth grinding	0	0
Hypoesthesia	0	0
Abnormal bleeding (nose, throat, bowels)	0	0
Abnormal vision	0	0
Paroniria	0	0
Yawning	0	0
Impaired concentration	1	0
Tremor	0	0
Dizziness	0	0
Insomnia	0	1
Agitation	0	2
Somnolence	0	0
Anorexia	0	0
Fatigue	0	0
Sweating	0	0
Dry mouth	0	0
Increase in sexual behavior	1	1
Male sexual dysfunction (if applicable)	0	0
Menstrual irregularity (if applicable)	0	0
Rash	1[a]	0
Urinary retention/changes to frequency	0	0
Tinnitus	0	0
Palpitation	0	0
Chest pain	0	0
Headache	1[b]	1[b]
Other	0	1[c]

[a]Heat rash, attributed to hot weather; [b]Same participant, headache experienced following each MRI scan underwent as part of the study design; [c]Dry Skin, attributed to cold weather.