Supplementary Online Materials - Tables S1 to S11

The acute and chronic cognitive and cerebral blood-flow effects of Nepalese Pepper (*Zanthoxylum armatum*) extract: a randomized, double-blind, placebo-controlled study in healthy humans

*Table S1. Factors derived from the cognitive tasks and **the global 'Speed of Performance' and 'Accuracy of Performance' outcomes** (averaged Z scores) derived from the entire battery. The top half of the table shows the data (mean plus SEM) related to the acute analysis of Day 1 data, and the bottom half of the table shows the data related to the chronic analysis of Day 56 data (plus Day 1 pre-dose baseline data). The ANOVA columns show the F scores and probabilities from the two-way ANOVA for that outcome: TxA = the treatment x assessment interaction term; T = the main effect of treatment term.*

DAY 1 (acute)

Measure		N	Baseline Day 1 pre-dose		1 hour		3 hour		6 hour			ANOVA	F	P
Speed of	pl	42	489.4	8.24	9.96	4.47	16.95	5.31	5.28	4.99		TxA	2.02	0.14
Attention (msec)	ZA	35	489.9	6.84	-2.95	4.90	-2.94	5.82	-3.01	5.46		T	4.43	0.04
Accuracy of	pl	42	77.12	1.60	-0.41	0.63	-1.32	0.81	-2.64	0.89		TxA	0.05	0.95
Attention (%)	ZA	35	76.59	1.48	-0.87	0.68	-2.11	0.89	-3.35	0.98		T	0.45	0.51
Working	pl	41	80.92	0.92	0.59	1.11	0.64	0.98	0.63	1.12		TxA	0.43	0.65
Memory (%)	ZA	38	79.48	1.08	-0.93	1.15	0.38	1.02	-0.68	1.16		T	0.63	0.43
Speed of	pl	41	911.8	23.0	-9.35	11.0	-23.3	11.9	-22.3	13.6		TxA	0.43	0.65
Memory (msec)	ZA	38	886.1	20.5	-19.7	11.4	-18.6	12.3	-30.7	14.1		T	0.11	0.74
Episodic	pl	42	60.24	1.33	-3.44	1.03	-4.20	1.23	-5.55	1.13		TxA	1.15	0.32
Memory (%)	ZA	39	59.48	1.37	-3.21	1.07	-6.36	1.28	-6.53	1.18		T	0.51	0.48
Accuracy of	pl	42	0.12	0.08	-0.12	0.05	-0.14	0.06	-0.24	0.06		TxA	1.63	0.20
Performance (z)	ZA	39	0.04	0.08	-0.10	0.05	-0.24	0.06	-0.32	0.06		T	0.53	0.47
Speed of	pl	42	0.03	0.09	0.03	0.05	0.04	0.05	-0.08	0.05		TxA	0.12	0.89
Performance (z)	ZA	39	0.13	0.09	-0.09	0.05	-0.09	0.05	-0.18	0.06		T	3.50	0.07

DAY 56 (chronic)

Measure			Baseline Day 1 pre-dose		Pre-dose		1 hour		3 hour		6 hour		ANOVA	F	P
Speed of	pl	38	489.6	8.89	4.24	7.12	9.34	6.34	12.11	5.97	7.51	5.98	TxA	1.11	0.35
Attention (msec)	ZA	35	489.9	6.84	-6.96	7.41	-10.2	6.61	-6.11	6.22	-0.88	6.23	T	3.18	0.08
Accuracy of	pl	38	77.97	1.68	0.46	0.92	-0.40	1.05	-1.16	1.03	-2.31	1.10	TxA	0.77	0.51
Attention (%)	ZA	35	76.59	1.48	0.70	0.96	1.26	1.09	-0.28	1.08	-1.52	1.14	T	0.43	0.51
Working	pl	38	80.99	0.97	-0.23	1.15	-0.27	1.19	-0.80	1.28	-0.68	1.25	TxA	0.42	0.74
Memory (%)	ZA	38	79.48	1.08	1.14	1.15	0.78	1.19	1.57	1.28	0.65	1.25	T	0.98	0.33
Speed of	pl	38	914.0	24.5	5.47	15.93	-13.4	15.6	-36.5	13.6	-44.0	16.5	TxA	0.54	0.66
Memory (msec)	ZA	38	886.1	20.5	-24.9	15.93	-23.4	15.6	-53.0	13.6	-45.7	16.5	T	0.78	0.38
Episodic	pl	39	60.46	1.37	1.94	1.06	-2.00	1.23	-3.56	1.08	-4.09	1.18	TxA	0.42	0.74
Memory (%)	ZA	39	59.48	1.37	1.98	1.06	-3.14	1.23	-4.51	1.08	-5.72	1.18	T	0.49	0.49
Accuracy of	pl	39	0.15	0.08	0.11	0.05	-0.03	0.06	-0.11	0.06	-0.16	0.07	TxA	0.23	0.87
Performance (z)	ZA	39	0.04	0.08	0.16	0.05	-0.01	0.06	-0.07	0.06	-0.17	0.07	T	0.13	0.71
Speed of	pl	39	0.02	0.09	-0.00	0.06	0.01	0.06	-0.06	0.06	-0.08	0.06	TxA	0.49	0.69
Performance (z)	ZA	39	0.13	0.09	-0.15	0.06	-0.20	0.06	-0.23	0.062	-0.19	0.06	T	4.77	0.03

Table S2. Acute Day 1 data for the individual cognitive task outcomes. Showing pre-dose Day 1 raw baseline data and post-dose change from baseline data (all mean plus SEM). The ANOVA columns show the F scores and probabilities from the two-way ANOVA for that outcome: TxA = the treatment x assessment interaction term; T = the main effect of treatment term.

Task		N	Baseline		Post-dose assessment						ANOVA		
			Day 1 pre-dose		1 hour post-dose		3 hour post-dose		6 hours post-dose			F	P
Immediate Word Recall (% correct)	pl	42	42.14	*2.03*	-4.60	*1.99*	-4.05	*2.26*	-4.92	*1.85*	TxA	0.37	0.69
	ZA	39	38.21	*2.10*	-2.22	*2.06*	-4.27	*2.34*	-3.59	*1.92*	T	0.25	0.62
Immediate Word recall (errors)	pl	42	4.13	*0.82*	0.79	*0.99*	-0.79	*1.09*	2.70	*1.17*	TxA	2.87	0.06
	ZA	39	4.79	*1.12*	0.00	*1.02*	1.37	*1.13*	1.37	*1.22*	T	0.00	0.99
Numeric Working Mem (% correct)	pl	41	95.53	*0.64*	0.46	*0.87*	1.74	*0.69*	0.27	*0.81*	TxA	1.16	0.32
	ZA	38	95.70	*0.69*	0.47	*0.91*	-0.20	*0.71*	-0.47	*0.85*	T	1.05	0.31
Numeric Working Mem RT (msecs)	pl	41	880.7	*24.6*	-44.8	*15.9*	-36.4	*15.5*	-42.5	*15.7*	TxA	0.67	0.51
	ZA	38	847.8	*25.5*	-57.2	*16.5*	-63.3	*16.1*	-76.8	*16.3*	T	1.55	0.22
Choice Reaction Time (% correct)	pl	42	98.33	*0.39*	-0.10	*0.46*	0.05	*0.34*	-0.29	*0.30*	TxA	0.51	0.60
	ZA	39	97.69	*0.55*	0.21	*0.48*	0.00	*0.35*	-0.56	*0.31*	T	0.00	0.98
Choice Reaction Time RT (msecs)	pl	42	482.2	*13.0*	14.91	*7.53*	27.09	*9.67*	11.60	*8.87*	TxA	1.10	0.34
	ZA	39	463.1	*10.4*	1.01	*7.81*	6.62	*10.04*	6.31	*9.20*	T	1.42	0.24
Corsi Span (capacity score)	pl	42	5.98	*0.14*	0.07	*0.16*	-0.04	*0.16*	0.08	*0.19*	TxA	1.65	0.19
	ZA	39	5.62	*0.19*	-0.16	*0.17*	0.12	*0.17*	-0.04	*0.19*	T	0.09	0.77
Peg and Ball think time (msecs)	pl	41	3518	*237*	-300	*140*	-682	*139*	-659	*161*	TxA	1.01	0.37
	ZA	38	3662	*227*	-449	*145*	-663	*145*	-840	*167*	T	0.29	0.59
Peg and Ball time (msecs)	pl	41	9740	*417*	-640	*227*	-1490	*232*	-1408	*257*	TxA	2.60	0.08
	ZA	38	10247	*471*	-833	*235*	-1040	*241*	-1297	*267*	T	0.16	0.69
Peg and Ball errors (number)	pl	42	3.21	*0.44*	0.45	*0.68*	-1.24	*0.53*	-0.31	*0.63*	TxA	3.49	0.03
	ZA	38	3.47	*0.53*	-0.21	*0.71*	0.03	*0.56*	1.18	*0.66*	T	0.92	0.34
Name to Face (% correct)	pl	42	65.08	*2.56*	0.00	*2.30*	-2.48	*2.39*	-4.27	*2.64*	TxA	0.09	0.91
	ZA	39	65.60	*2.41*	-6.41	*2.39*	-8.97	*2.48*	-9.40	*2.74*	T	4.36	0.04
Name to Face (msecs)	pl	42	10661	*567*	-358	*706*	-316	*695*	-1115	*758*	TxA	0.50	0.61
	ZA	39	11614	*656*	-1253	*732*	-245	*722*	-1710	*786*	T	0.30	0.59
Delayed word recall (% correct)	pl	42	27.54	*2.18*	-10.9	*2.31*	-12.22	*2.38*	-15.24	*2.26*	TxA	2.63	0.11
	ZA	39	23.59	*2.21*	-4.96	*2.40*	-11.03	*2.47*	-9.15	*2.34*	T	1.36	0.26
Delayed word recall (errors)	pl	42	7.62	*1.34*	5.56	*1.84*	5.24	*1.80*	8.41	*2.42*	TxA	3.36	0.04
	ZA	39	7.52	*1.51*	0.00	*1.91*	7.35	*1.86*	5.47	*2.51*	T	0.80	0.37
Word Recog'tion (% correct)	pl	42	73.65	*1.51*	-1.75	*1.62*	-1.03	*1.68*	-2.38	*1.81*	TxA	3.03	0.05
	ZA	39	75.04	*1.71*	-0.34	*1.68*	-3.25	*1.74*	-6.15	*1.88*	T	0.52	0.47
Word Recog'tion RT (msecs)	pl	42	984.4	*36.1*	-15.1	*23.70*	-54.84	*23.38*	-32.49	*28.32*	TxA	0.18	0.83
	ZA	39	950.4	*32.9*	0.41	*24.60*	-34.50	*24.26*	-32.77	*29.39*	T	0.16	0.69
Picture Recog'ion (% correct)	pl	42	92.78	*1.21*	0.00	*1.17*	-1.19	*1.21*	-0.95	*1.24*	TxA	0.36	0.70
	ZA	39	94.96	*1.02*	-2.14	*1.21*	-4.27	*1.25*	-4.36	*1.29*	T	3.73	0.06
Picture Recog'ion (msecs)	pl	42	869.4	*21.1*	34.06	*22.77*	23.57	*23.80*	1.96	*18.90*	TxA	0.89	0.41
	ZA	39	869.6	*19.8*	9.28	*23.63*	40.48	*24.70*	15.42	*19.61*	T	0.01	0.94

Table S3. Chronic Day 56 data for the individual cognitive task outcomes. Showing pre-dose Day 1 raw baseline data and Day 56 change from baseline data (all means plus SEM). The ANOVA columns show the F scores and probabilities from the two-way ANOVA for that outcome: TxA = the treatment x assessment interaction term; T = the main effect of treatment term.

		N	Baseline		Day 56 assessment								ANOVA	
			Day 1 Pre-dose		Pre-dose		1 hr post-dose		3 hr post-dose		6 hr post-dose		F	P
Immediate Word Recall (% correct)	pl	39	42.65	2.14	1.11	1.75	1.03	1.99	-1.28	2.01	-2.56	2.22	TxA 0.37	0.78
	ZA	39	38.21	2.10	3.16	2.27	-0.26	2.35	-1.37	1.88	-2.39	1.83	T 0.01	0.92
Immediate Word recall (errors)	pl	39	4.10	0.87	0.51	1.08	-1.03	1.08	1.20	1.27	0.51	1.02	TxA 0.84	0.47
	ZA	39	4.79	1.12	-1.20	1.29	-0.51	1.11	-0.68	0.88	0.00	1.12	T 0.59	0.44
Numeric Working Mem (% correct)	pl	38	95.41	0.68	1.20	0.68	1.32	0.60	0.94	0.79	1.29	0.82	TxA 0.80	0.50
	ZA	38	95.70	0.69	1.40	0.70	0.29	0.78	0.82	0.85	0.53	0.78	T 0.22	0.64
Numeric Working Mem RT (msecs)	pl	38	872.8	25.8	-11.8	19.87	-42.8	19.97	-58.0	19.63	-49.7	22.25	TxA 0.81	0.49
	ZA	38	847.8	25.5	-31.1	16.51	-86.7	17.37	-76.5	17.06	-94.3	15.54	T 2.01	0.16
Choice Reaction Time (% correct)	pl	39	98.41	0.40	0.00	0.40	-0.26	0.36	0.51	0.42	-0.05	0.38	TxA 0.68	0.56
	ZA	39	97.69	0.55	0.10	0.52	0.00	0.47	0.31	0.54	0.51	0.54	T 0.10	0.75
Choice Reaction Time RT (msecs)	pl	39	486.1	13.8	11.63	12.34	15.38	12.48	20.51	11.85	13.56	10.94	TxA 0.64	0.59
	ZA	39	463.1	10.4	9.21	12.78	-0.06	10.73	5.69	9.42	11.08	9.29	T 0.40	0.53
Corsi Span (capacity score)	pl	39	6.00	0.15	-0.15	0.21	-0.18	0.23	-0.22	0.26	-0.22	0.26	TxA 0.42	0.74
	ZA	39	5.62	0.19	0.11	0.17	0.17	0.19	0.26	0.19	0.13	0.16	T 1.78	0.19
Peg and Ball think time (msecs)	pl	38	3582	235	-624	189	-854	186	-857	182	-1122	171	TxA 1.58	0.20
	ZA	38	3662	227	-383	189	-828	186	-998	182	-1057	171	T 0.04	0.84
Peg and Ball time (msecs)	pl	38	9760	439	-1194	324	-1527	344	-1374	371	-1762	388	TxA 4.71	0.00
	ZA	38	10247	471	-442	324	-1454	344	-1896	371	-2117	388	T 0.00	0.98
Peg and Ball errors (number)	pl	39	3.33	0.46	-1.15	0.53	-0.33	0.73	0.67	0.67	-0.23	0.63	TxA 0.55	0.65
	ZA	38	3.47	0.53	-0.74	0.65	-0.79	0.65	-0.03	0.61	-0.29	0.74	T 0.07	0.79
Name to Face (% correct)	pl	39	65.28	2.73	0.32	2.33	-3.74	2.20	-4.91	2.44	-6.52	2.24	TxA 1.08	0.30
	ZA	39	65.60	2.41	-1.82	2.87	-8.33	3.28	-8.01	2.45	-8.87	2.74	T 0.19	0.90
Name to Face (msecs)	pl	39	10720	598	-1446	561	-146	826	-1038	704	-189	760	TxA 1.76	0.16
	ZA	39	11614	656	-1034	561	-1755	826	-1940	704	-1845	760	T 1.38	0.24
Delayed word recall (% correct)	pl	39	27.95	2.28	4.02	2.02	-8.89	1.84	-9.40	2.61	-9.91	2.29	TxA 0.96	0.41
	ZA	39	23.59	2.21	6.41	2.24	-4.44	2.34	-10.26	1.81	-9.83	2.07	T 0.46	0.50
Delayed word recall (errors)	pl	39	7.35	1.38	0.51	1.42	2.22	1.46	3.59	1.91	5.98	2.48	TxA 0.37	0.77
	ZA	39	7.52	1.51	-1.03	1.26	2.91	2.28	4.44	1.95	4.96	2.43	T 0.01	0.91
Word Recog'tion (% correct)	pl	39	73.25	1.48	3.50	1.38	1.54	1.43	-0.51	1.80	1.11	1.60	TxA 1.98	0.12
	ZA	39	75.04	1.71	2.22	1.48	-0.34	1.94	0.51	1.59	-3.33	2.05	T 0.73	0.39
Word Recog'tion RT (msecs)	pl	39	995.0	38.4	-43.5	30.40	-24.9	25.39	-75.00	28.59	-78.8	32.58	TxA 0.27	0.85
	ZA	39	950.4	32.9	-40.9	21.27	7.03	30.48	-71.50	25.29	-58.8	28.28	T 0.21	0.65
Picture Recog'ion (% correct)	pl	39	93.16	1.26	0.77	1.26	0.08	1.32	-1.71	1.36	-2.57	1.26	TxA 0.36	0.78
	ZA	39	94.96	1.02	-0.09	0.94	-2.31	1.26	-3.42	1.19	-4.19	1.35	T 1.18	0.28
Picture Recog'ion (msecs)	pl	39	872.9	22.3	67.51	39.04	27.32	18.35	27.56	19.77	-2.21	21.41	TxA 1.32	0.27
	ZA	39	869.6	19.8	13.73	24.75	6.59	21.62	-11.94	20.34	21.32	23.04	T 0.94	0.33

Table S4. Bond-Lader mood scale outcomes. The top half of the table shows the data (mean plus SEM) related to the acute analysis of Day 1 data, and the bottom half of the table shows the data related to the chronic analysis of Day 56 data (plus Day 1 pre-dose baseline data). The ANOVA columns show the F scores and probabilities from the two-way ANOVA for that outcome: TxA = the treatment x assessment interaction term; T = the main effect of treatment term.

Day 1 (acute)

Bond-Lader factor			Baseline Day 1 pre-dose		Post-dose Assessment 1 hour		3 hour		6 hour			ANOVA	F	P
Alert	pl	42	68.42	2.17	-2.48	1.54	-9.65	2.22	-8.35	2.21		TxA	0.29	0.75
	ZA	39	67.25	2.26	-1.89	1.60	-9.60	2.31	-6.33	2.30		T	0.13	0.72
Calm	pl	42	71.61	2.23	-1.52	1.72	-2.61	1.76	-1.31	1.81		TxA	0.07	0.93
	ZA	39	67.62	2.34	-1.65	1.78	-2.99	1.83	-0.86	1.87		T	0.00	0.99
Content	pl	42	75.56	1.92	-1.95	1.00	-3.15	1.53	-3.80	1.33		TxA	3.58	0.03
	ZA	39	74.06	2.42	-0.44	1.03	-5.68	1.59	-2.05	1.38		T	0.02	0.88

Day 56 (chronic)

Bond-Lader factor			Baseline Day 1 pre-dose		Day 56 assessment Pre-dose		1 hour		3 hour		6 hour			F	P
Alert	pl	39	67.65	2.08	0.58	1.70	-2.33	1.80	-4.64	1.92	-4.87	2.17	TxA	2.45	0.06
	ZA	39	67.25	2.26	0.09	2.18	-2.51	1.90	-9.50	2.88	-3.03	1.72	T	0.14	0.71
Calm	pl	39	70.06	2.18	-0.09	2.20	-0.04	2.37	0.33	2.06	-1.63	2.47	TxA	1.23	0.30
	ZA	39	67.62	2.34	0.26	1.51	-0.74	1.89	-3.60	2.21	-4.33	1.73	T	0.48	0.49
Content	pl	39	74.43	1.93	-0.63	1.28	-2.00	1.32	-2.62	1.34	-1.97	1.45	TxA	1.54	0.21
	ZA	39	74.06	2.42	-0.40	1.89	-0.85	1.95	-5.17	2.41	-0.90	1.63	T	0.00	0.99

Table S5. Acute Day 1 data for the Cognitive Demand Battery outcomes. Showing raw data for the three pre-dose Day 1 baseline repetitions of the battery and change from baseline data for the 3 repetitions of the Cognitive Demand Battery at each post-dose assessment (all mean plus SEM). The ANOVA columns show the F scores and probabilities from the two-way ANOVA for that outcome: TxA = the treatment x assessment interaction term; T = the main effect of treatment term.

outcome		N	Baseline Pre-dose			Assessment (change from baseline data)									ANOVA		
			Rep 1	Rep 2	Rep 3	1-hour post-dose Rep 1	Rep 2	Rep 3	3-hour post-dose Rep 1	Rep 2	Rep 3	6-hour post-dose Rep 1	Rep 2	Rep 3		F	P
Mental Fatigue (mm)	pl	42	47.79 *2.85*	49.79 *3.29*	58.40 *3.42*	4.86 *2.40*	11.7 *2.47*	6.55 *2.32*	17.36 *2.77*	20.71 *2.92*	14.88 *2.72*	17.79 *3.25*	23.98 *2.86*	19.07 *2.36*	TxA	0.28	0.75
	ZA	39	55.95 *3.17*	64.15 *3.02*	70.82 *2.89*	4.39 *2.49*	5.03 *2.56*	0.28 *2.41*	13.18 *2.87*	12.56 *3.03*	10.51 *2.82*	16.51 *3.38*	12.64 *2.97*	12.13 *2.45*	T	3.45	0.07
RVIP % correct	pl	42	58.57 *3.17*	55.06 *3.32*	54.11 *3.49*	-1.4 *2.07*	-1.43 *1.68*	0.66 *1.88*	-2.98 *2.11*	-3.27 *2.02*	-1.79 *2.17*	-5.00 *2.46*	-6.96 *2.08*	-3.04 *2.15*	TxA	0.02	0.97
	ZA	35	53.36 *3.52*	55.00 *3.14*	56.50 *2.71*	2.71 *2.26*	-2.50 *1.84*	-4.6 *2.06*	1.29 *2.31*	-5.79 *2.22*	-7.14 *2.37*	-2.00 *2.70*	-6.57 *2.28*	-9.29 *2.35*	T	0.27	0.61
RVIP RT msec	pl	42	490.3 *8.16*	497.9 *8.15*	501.9 *8.55*	4.34 *5.54*	9.30 *4.92*	1.41 *5.68*	9.16 *5.37*	10.71 *5.77*	0.54 *6.47*	3.84 *7.00*	-2.49 *6.15*	-4.47 *7.17*	TxA	1.08	0.34
	ZA	35	509.4 *7.18*	514.2 *8.11*	528.2 *8.87*	-0.5 *6.07*	3.52 *5.38*	-11.3 *6.23*	-2.92 *5.88*	-6.28 *6.32*	-14.2 *7.08*	-13.4 *7.67*	-7.48 *6.73*	-7.81 *7.86*	T	3.80	0.05
RVIP FA No.	pl	42	2.45 *0.34*	1.57 *0.28*	1.38 *0.19*	-1.45 *0.48*	0.00 *0.29*	0.05 *0.27*	-1.17 *0.50*	0.19 *0.31*	-0.19 *0.27*	-0.98 *0.45*	-0.02 *0.34*	0.24 *0.37*	TxA	0.20	0.82
	ZA	35	3.51 *0.72*	3.00 *0.45*	2.51 *0.37*	-1.97 *0.53*	-0.74 *0.32*	-0.63 *0.30*	-1.91 *0.55*	-0.71 *0.34*	-0.34 *0.29*	-1.89 *0.50*	-0.86 *0.38*	-0.34 *0.41*	T	5.25	0.02
Serial 3 Correct No.	pl	41	33.15 *2.27*	35.98 *2.41*	36.37 *2.30*	4.44 *0.86*	2.29 *0.96*	1.00 *1.05*	5.63 *1.07*	2.54 *1.02*	1.85 *1.14*	5.12 *1.04*	3.20 *1.08*	2.39 *1.25*	TxA	1.06	0.35
	ZA	39	32.54 *2.32*	34.15 *2.33*	34.08 *2.41*	4.03 *0.88*	2.80 *0.99*	1.62 *1.08*	4.36 *1.10*	3.08 *1.05*	3.15 *1.17*	4.10 *1.07*	1.05 *1.10*	2.21 *1.28*	T	0.07	0.79
Serial 3 Error No.	pl	41	1.46 *0.27*	2.15 *0.35*	1.80 *0.31*	0.78 *0.38*	0.10 *0.47*	0.37 *0.47*	0.61 *0.43*	-0.56 *0.35*	-0.42 *0.42*	0.63 *0.46*	-0.61 *0.44*	-0.10 *0.42*	TxA	1.09	0.34
	ZA	39	2.15 *0.38*	2.33 *0.37*	2.79 *0.42*	0.59 *0.39*	0.26 *0.48*	0.08 *0.48*	0.90 *0.45*	-0.36 *0.36*	-0.49 *0.43*	0.74 *0.48*	0.59 *0.45*	-0.26 *0.43*	T	0.16	0.69
Serial 3 Total No.	pl	41	34.61 *2.24*	38.12 *2.34*	38.17 *2.29*	5.22 *0.77*	2.39 *0.79*	1.37 *0.91*	6.24 *0.93*	1.98 *0.96*	1.44 *0.99*	5.76 *0.88*	2.59 *0.94*	2.29 *1.19*	TxA	0.79	0.46
	ZA	39	34.69 *2.24*	36.49 *2.33*	36.87 *2.40*	4.62 *0.79*	3.05 *0.81*	1.69 *0.93*	5.26 *0.95*	2.72 *0.98*	2.67 *1.01*	4.85 *0.90*	1.64 *0.97*	1.95 *1.22*	T	0.01	0.91
Serial 7 Correct No.	pl	41	20.90 *1.91*	22.83 *2.00*	21.90 *1.84*	2.32 *0.77*	1.49 *0.67*	2.27 *0.80*	4.05 *0.82*	1.46 *0.83*	3.15 *0.91*	4.66 *0.79*	1.51 *0.93*	4.17 *0.85*	TxA	2.33	0.10
	ZA	39	19.67 *1.67*	21.21 *1.80*	19.69 *1.77*	2.33 *0.79*	1.08 *0.69*	1.44 *0.82*	4.15 *0.84*	1.85 *0.85*	3.87 *0.94*	2.67 *0.81*	1.00 *0.95*	3.28 *0.87*	T	0.24	0.62
Serial 7 Error No.	pl	41	2.39 *0.30*	2.22 *0.34*	2.49 *0.33*	0.12 *0.45*	0.15 *0.35*	0.27 *0.46*	0.00 *0.42*	0.27 *0.57*	-0.71 *0.53*	-0.44 *0.37*	0.49 *0.48*	-0.44 *0.48*	TxA	0.07	0.93
	ZA	39	2.67 *0.44*	2.56 *0.33*	3.90 *0.54*	0.51 *0.46*	0.44 *0.36*	-0.03 *0.47*	-0.08 *0.43*	0.44 *0.58*	-0.51 *0.55*	0.36 *0.38*	0.82 *0.49*	-0.85 *0.50*	T	0.18	0.68
Serial 7 Total No.	pl	41	23.29 *1.85*	25.05 *1.96*	24.39 *1.84*	2.44 *0.68*	1.63 *0.60*	2.54 *0.66*	4.05 *0.69*	1.73 *0.74*	2.44 *0.76*	4.22 *0.72*	2.00 *0.74*	3.73 *0.68*	TxA	2.79	0.06
	ZA	39	22.33 *1.56*	23.77 *1.71*	23.59 *1.63*	2.85 *0.69*	1.51 *0.62*	1.41 *0.67*	4.08 *0.70*	2.28 *0.75*	3.36 *0.78*	3.03 *0.74*	1.82 *0.76*	2.44 *0.70*	T	0.12	0.73

Table S6 (part 1). Chronic Day 56 data for the Cognitive Demand Battery outcomes. Showing raw data for the three pre-dose Day 1 baseline repetitions of the battery (part 1) and change from baseline data for the the 3 repetitions of the Cognitive Demand Battery during the Day 56 pre-dose assessment (part 1) and the 1 hour, 3 hour and 6 hour post-dose assessments (part 2) (all mean plus SEM). The ANOVA columns show the F scores and probabilities from the two-way ANOVA for that outcome: TxA = the treatment x assessment interaction term; T = the main effect of treatment term.

| outcome | | N | Day 1 Baseline | | | | | | Day 56 Assessment (change from baseline) | | | | | |
| | | | Baseline assessment (pre-dose) | | | | | | Pre-dose | | | | | |
			Rep 1		Rep 2		Rep 3		Rep 1		Rep 2		Rep 3	
Mental Fatigue (mm)	pl	39	48.1	2.98	49.5	3.36	58.4	3.52	-5.54	3.20	-1.31	3.10	-3.77	3.39
	ZA	39	55.9	3.17	64.2	3.02	70.8	2.89	-7.13	3.20	-10.6	3.10	-12.9	3.39
RVIP % correct	pl	38	58.56	3.33	56.06	3.41	54.75	3.63	-2.30	2.09	1.91	2.20	3.16	2.55
	ZA	35	53.36	3.52	55.00	3.14	56.50	2.71	5.57	2.18	2.29	2.29	-2.14	2.66
RVIP RT msec	pl	38	489.6	8.53	497.7	8.56	499.3	8.78	-1.23	6.55	0.52	6.18	7.24	7.69
	ZA	35	509.4	7.18	514.2	8.11	528.2	8.87	-12.4	6.83	-10.1	6.44	-20.6	8.01
RVIP FA No.	pl	38	2.45	0.34	1.63	0.29	1.40	0.20	-0.21	0.52	-0.16	0.32	-0.32	0.30
	ZA	35	3.51	0.72	3.00	0.45	2.51	0.37	-1.26	0.54	-0.86	0.33	-0.31	0.31
Serial 3 Correct No.	pl	38	33.56	2.37	36.54	2.50	36.90	2.37	4.47	1.06	3.32	1.03	2.95	1.11
	ZA	39	32.54	2.32	34.15	2.33	34.08	2.41	3.80	1.04	3.67	1.01	3.59	1.09
Serial 3 Error No.	pl	38	1.36	0.28	2.13	0.36	1.74	0.32	0.00	0.37	-0.63	0.44	0.17	0.45
	ZA	39	2.15	0.38	2.33	0.37	2.79	0.42	0.00	0.37	0.21	0.43	-0.21	0.45
Serial 3 Total No.	pl	38	34.92	2.35	38.67	2.43	38.64	2.37	4.47	0.97	2.68	0.94	3.12	1.06
	ZA	39	34.69	2.24	36.49	2.33	36.87	2.40	3.80	0.96	3.87	0.92	3.39	1.05
Serial 7 Correct No.	pl	38	21.31	1.97	23.10	2.07	22.33	1.89	1.92	0.81	1.68	0.73	2.58	0.92
	ZA	39	19.67	1.67	21.21	1.80	19.69	1.77	1.21	0.80	1.05	0.72	3.05	0.90
Serial 7 Error No.	pl	38	2.28	0.30	2.18	0.34	2.41	0.34	-0.51	0.44	-0.16	0.39	-0.21	0.55
	ZA	39	2.67	0.44	2.56	0.33	3.90	0.54	0.44	0.43	0.51	0.39	-0.82	0.54
Serial 7 Total No.	pl	38	23.59	1.91	25.28	2.04	24.74	1.89	1.41	0.72	1.53	0.68	2.37	0.83
	ZA	39	22.33	1.56	23.77	1.71	23.59	1.63	1.64	0.71	1.56	0.67	2.23	0.82

Continued – Table S6. (part 2)….

Day 56 Assessment (change from baseline)

Measure		N	1-hour post-dose						3-hour post-dose						6-hour post-dose						ANOVA	F	P
			Rep 1		Rep 2		Rep 3		Rep 1		Rep 2		Rep 3		Rep 1		Rep 2		Rep 3				
Mental Fatigue (mm)	pl	39	5.97	*3.12*	13.59	*3.04*	5.77	*3.21*	11.31	*3.20*	16.59	*3.36*	11.87	*3.30*	18.26	*3.12*	22.23	*3.35*	17.82	*3.20*	TxA	1.88	0.13
	ZA	39	0.44	*3.12*	-3.05	*3.04*	-6.39	*3.21*	7.95	*3.20*	4.41	*3.36*	1.46	*3.30*	8.10	*3.12*	7.08	*3.35*	2.13	*3.20*	T	8.01	0.01
RVIP % correct	pl	38	-0.07	*2.64*	-0.72	*2.45*	-0.99	*2.52*	-2.96	*2.86*	-3.09	*2.13*	-2.83	*2.37*	-3.75	*2.73*	-4.08	*2.56*	-5.72	*2.69*	TxA	0.87	0.46
	ZA	35	7.57	*2.75*	1.00	*2.56*	0.71	*2.62*	4.57	*2.98*	-1.36	*2.22*	-3.86	*2.47*	3.00	*2.84*	-4.07	*2.67*	-7.71	*2.81*	T	0.70	0.41
RVIP RT msec	pl	38	2.96	*7.46*	4.55	*6.11*	1.72	*6.31*	1.73	*8.43*	3.74	*6.78*	1.19	*7.20*	5.01	*8.74*	-1.57	*7.41*	-2.44	*6.39*	TxA	3.74	0.06
	ZA	35	-12.0	*7.77*	-4.92	*6.36*	-22.1	*6.58*	-11.9	*8.78*	-5.20	*7.06*	-10.6	*7.50*	-2.33	*9.11*	-8.94	*7.72*	-14.5	*6.66*	T	0.82	0.48
RVIP FA No.	pl	38	-1.45	*0.50*	-0.32	*0.35*	-0.21	*0.35*	-1.24	*0.48*	-0.63	*0.36*	-0.21	*0.31*	-1.24	*0.52*	-0.68	*0.40*	-0.11	*0.35*	TxA	3.24	0.08
	ZA	35	-1.89	*0.52*	-1.03	*0.36*	-0.80	*0.36*	-2.14	*0.50*	-1.37	*0.37*	-0.77	*0.32*	-2.14	*0.55*	-1.14	*0.42*	-0.51	*0.36*	T	0.11	0.95
Serial 3 Correct No.	pl	38	7.74	*1.06*	4.82	*1.17*	4.45	*1.39*	7.03	*1.08*	2.95	*1.09*	2.55	*1.45*	7.76	*0.95*	4.00	*1.28*	3.45	*1.64*	TxA	6.42	0.00
	ZA	39	7.82	*1.05*	4.90	*1.15*	3.72	*1.37*	8.08	*1.07*	7.49	*1.08*	6.85	*1.44*	6.85	*0.94*	3.92	*1.27*	2.28	*1.62*	T	0.32	0.57
Serial 3 Error No.	pl	38	0.97	*0.55*	-0.21	*0.47*	-0.24	*0.49*	0.74	*0.45*	-0.16	*0.42*	0.61	*0.51*	0.21	*0.47*	-0.42	*0.56*	0.13	*0.67*	TxA	2.11	0.10
	ZA	39	0.92	*0.54*	0.74	*0.47*	0.90	*0.48*	0.69	*0.44*	-0.13	*0.42*	0.03	*0.50*	1.21	*0.46*	0.49	*0.55*	0.41	*0.66*	T	0.73	0.40
Serial 3 Total No.	pl	38	8.71	*1.01*	4.61	*1.13*	4.21	*1.21*	7.76	*1.05*	2.79	*1.09*	3.16	*1.36*	7.97	*0.96*	3.58	*1.17*	3.58	*1.58*	TxA	5.03	0.00
	ZA	39	8.74	*0.99*	5.64	*1.12*	4.62	*1.19*	8.77	*1.03*	7.36	*1.08*	6.87	*1.34*	8.05	*0.95*	4.41	*1.15*	2.69	*1.56*	T	0.73	0.40
Serial 7 Correct No.	pl	38	4.18	*0.88*	2.87	*0.70*	3.55	*1.08*	5.45	*0.94*	3.82	*0.91*	3.45	*1.00*	6.13	*0.98*	3.89	*0.89*	3.55	*1.23*	TxA	1.12	0.34
	ZA	39	3.10	*0.87*	2.74	*0.69*	4.64	*1.06*	5.05	*0.93*	4.36	*0.90*	5.10	*0.99*	5.41	*0.97*	1.85	*0.87*	3.51	*1.22*	T	0.04	0.84
Serial 7 Error No.	pl	38	-0.16	*0.57*	-0.21	*0.52*	0.40	*0.73*	-0.55	*0.41*	-0.42	*0.46*	-0.11	*0.60*	-0.34	*0.49*	-0.18	*0.58*	0.18	*0.89*	TxA	1.24	0.30
	ZA	39	1.67	*0.56*	1.03	*0.51*	-0.26	*0.72*	0.46	*0.41*	0.56	*0.45*	0.13	*0.59*	0.64	*0.49*	1.92	*0.57*	0.82	*0.88*	T	2.00	0.16
Serial 7 Total No.	pl	38	4.03	*0.89*	2.66	*0.67*	3.95	*0.94*	4.90	*0.88*	3.40	*0.86*	3.34	*0.94*	5.79	*0.88*	3.71	*0.82*	3.74	*1.27*	TxA	1.14	0.33
	ZA	39	4.77	*0.88*	3.77	*0.66*	4.39	*0.92*	5.51	*0.86*	4.92	*0.85*	5.23	*0.93*	6.05	*0.87*	3.77	*0.81*	4.33	*1.25*	T	0.48	0.49

Table S7. State-Trait Anxiety Inventory. Showing data (average plus SEM) for the pre-dose assessments on Day 1 and Day 56. The ANOVA columns show the F scores and probabilities from the two-way ANOVA for that outcome: DxT = the day x treatment interaction term; T = the main effect of treatment term.

| | | N | Visit | | | | ANOVA | | |
			Day 1		Day 56			F	T
State-Trait Anxiety Inventory (state)	pl	39	29.49	*1.10*	30.38	*1.14*	DxT	0.25	0.62
	ZA	40	31.78	*1.24*	31.93	*1.06*	T	1.804	0.183

Table S8. Acute effects of ZA on cerebral blood-flow parameters (total haemoglobin, deoxygenated haemoglobin, oxygenated haemoglobin, % oxygen saturation) on Day 1. Data are means (plus SEM). Pre-dose baseline data and data from each individual post-dose epoch are presented. The probability from the planned comparisons (P) between treatments at each epoch are also shown.

		Total Haemoglobin (µM)					Deoxygenated Haemoglobin (µM)					Oxygenated haemoglobin (µM)					% oxygen saturation				
		placebo		ZA		P	placebo		ZA		P	placebo		ZA		P	placebo		ZA		P
	Pre-dose Baseline	35.7	*1.50*	40.52	*2.10*		12.6	*0.59*	13.60	*0.83*		23.07	*1.38*	26.92	*1.48*		64.70	*1.28*	66.30	*1.24*	
Post-dose task epoch (change from baseline)	**Rest 1**	-0.27	*0.85*	-0.49	*0.83*	ns	0.31	*0.30*	0.07	*0.29*	ns	-0.58	*0.65*	-0.55	*0.64*	ns	-0.95	*0.47*	-0.63	*0.46*	ns
	Rest 2	-0.39	*0.87*	-0.57	*0.85*	ns	0.28	*0.28*	-0.08	*0.27*	ns	-0.67	*0.67*	-0.49	*0.65*	ns	-1.01	*0.43*	-0.30	*0.42*	0.002
	3s	-0.04	*0.92*	-0.62	*0.89*	< 0.001	0.25	*0.31*	-0.09	*0.30*	ns	-0.29	*0.70*	-0.54	*0.68*	ns	-0.63	*0.49*	-0.39	*0.48*	ns
	7s	0.06	*0.94*	-0.53	*0.92*	< 0.001	0.06	*0.32*	-0.23	*0.32*	ns	0.00	*0.72*	-0.29	*0.70*	ns	-0.03	*0.51*	0.05	*0.50*	ns
	RVIP 1	0.00	*0.93*	-0.94	*0.91*	< 0.001	-0.06	*0.32*	-0.29	*0.31*	ns	0.07	*0.69*	-0.66	*0.67*	< 0.001	0.24	*0.46*	-0.17	*0.45*	ns
	RVIP 2	0.00	*0.93*	-0.96	*0.91*	< 0.001	-0.12	*0.33*	-0.30	*0.32*	ns	0.13	*0.68*	-0.66	*0.67*	< 0.001	0.38	*0.47*	-0.15	*0.46*	ns
	3s	0.02	*0.95*	-0.61	*0.93*	< 0.001	-0.02	*0.32*	-0.35	*0.31*	ns	0.04	*0.72*	-0.26	*0.70*	ns	0.18	*0.50*	0.21	*0.49*	ns
	7s	0.02	*0.96*	-0.65	*0.93*	< 0.001	-0.09	*0.33*	-0.41	*0.32*	ns	0.11	*0.73*	-0.24	*0.71*	ns	0.31	*0.51*	0.34	*0.50*	ns
	RVIP 1	-0.04	*0.96*	-0.80	*0.93*	< 0.001	-0.22	*0.35*	-0.57	*0.34*	ns	0.18	*0.71*	-0.23	*0.69*	ns	0.60	*0.54*	0.58	*0.53*	ns
	RVIP 2	0.04	*1.00*	-0.91	*0.97*	< 0.001	-0.19	*0.36*	-0.49	*0.35*	ns	0.24	*0.73*	-0.42	*0.71*	< 0.001	0.59	*0.54*	0.32	*0.52*	ns
	3s	0.12	*0.95*	-0.42	*0.92*	< 0.001	0.00	*0.31*	-0.39	*0.31*	ns	0.12	*0.74*	-0.03	*0.72*	ns	0.21	*0.56*	0.48	*0.55*	ns
	7s	0.14	*0.99*	-0.33	*0.97*	0.01	-0.04	*0.33*	-0.39	*0.32*	ns	0.17	*0.78*	0.06	*0.76*	ns	0.33	*0.58*	0.57	*0.56*	ns
	RVIP 1	0.13	*0.99*	-0.67	*0.96*	< 0.001	-0.23	*0.34*	-0.47	*0.33*	ns	0.36	*0.75*	-0.19	*0.73*	0.002	0.82	*0.55*	0.53	*0.54*	ns
	RVIP 2	0.10	*1.01*	-0.82	*0.98*	< 0.001	-0.24	*0.35*	-0.54	*0.34*	ns	0.34	*0.77*	-0.28	*0.75*	< 0.001	0.79	*0.55*	0.57	*0.54*	ns

Table S9. Global effects of ZA on cerebral blood-flow parameters (total haemoglobin, deoxygenated haemoglobin, oxygenated haemoglobin, % oxygen saturation). Pre-dose and post-dose resting raw data (mean plus SEM) from Day 1 and Day 56 are presented. The ANOVA columns show the F scores and probabilities from the two-way ANOVA for each outcome: DxT = the day x treatment interaction term; T = the main effect of treatment term.

		Day 1				Day 56				ANOVA		
		Pre-dose		Post-dose		Pre-dose		Post-dose			F	P
Deoxygenated Haemoglobin	placebo	12.16	*0.73*	12.42	*0.65*	12.11	*0.71*	12.42	*0.66*	DxT	0.28	0.60
	ZA	13.50	*0.71*	13.55	*0.64*	13.20	*0.70*	13.35	*0.64*	T	1.54	0.22
Oxygenated haemoglobin	placebo	23.47	*1.55*	22.79	*1.32*	24.47	*1.63*	23.47	*1.35*	DxT	2.18	0.15
	ZA	27.00	*1.51*	26.30	*1.29*	26.35	*1.59*	25.40	*1.32*	T	1.99	0.17
Total Haemoglobin	placebo	35.47	*2.01*	35.21	*1.72*	36.58	*2.12*	35.79	*1.82*	DxT	2.47	0.12
	ZA	40.50	*1.96*	39.95	*1.67*	39.55	*2.06*	38.90	*1.77*	T	2.44	0.13
% oxygen saturation	placebo	64.79	*1.28*	63.89	*1.21*	66.11	*1.29*	64.89	*1.13*	DxT	2.14	0.15
	ZA	66.30	*1.25*	65.75	*1.18*	65.90	*1.25*	65.15	*1.11*	T	0.29	0.59

Table S10. Acute and chronic effects of ZA on haemodynamic responses to task performance. *Mean (plus SEM) data for each cerebral blood-flow parameter (total haemoglobin, deoxygenated haemoglobin, oxygenated haemoglobin, % oxygen saturation) for the immediately pre-task resting baseline and for each task performance epoch are presented. The probability from the planned comparisons (P) between treatments at each epoch are also shown.*

		Oxygenated haemoglobin					Deoxygenated Haemoglobin					Total Haemoglobin					% oxygen saturation				
		Placebo		ZA		P	Placebo		ZA		P	Placebo		ZA		P	Placebo		ZA		P
DAY 1																					
Resting baseline		22.79	1.32	26.30	1.29		12.42	0.65	13.55	0.64		35.21	1.72	39.95	1.67		63.89	1.21	65.75	1.18	
Task epoch (change from resting baseline data)	**3s**	0.28	0.15	-0.02	0.16	ns	0.01	0.07	-0.08	0.07	ns	0.28	0.15	-0.10	0.16	0.006	0.23	0.19	-0.03	0.17	ns
	7s	0.53	0.21	0.23	0.22	ns	-0.19	0.09	-0.23	0.09	ns	0.34	0.19	0.00	0.20	0.031	0.78	0.26	0.29	0.24	ns
	RVIP 1	0.59	0.20	-0.13	0.20	<0.001	-0.30	0.10	-0.28	0.10	ns	0.30	0.18	-0.42	0.18	<0.001	1.04	0.26	0.57	0.21	<0.001
	RVIP 2	0.68	0.23	-0.14	0.23	<0.001	-0.35	0.10	-0.30	0.11	ns	0.33	0.22	-0.43	0.22	<0.001	1.20	0.29	0.68	0.24	<0.001
	3s	0.52	0.26	0.26	0.26	ns	-0.29	0.11	-0.35	0.11	ns	0.23	0.24	-0.09	0.25	0.050	0.94	0.31	0.59	0.30	ns
	7s	0.62	0.25	0.28	0.26	0.039	-0.36	0.11	-0.40	0.12	ns	0.26	0.25	-0.12	0.26	0.005	1.13	0.31	0.67	0.31	ns
	RVIP 1	0.74	0.24	0.29	0.24	0.001	-0.46	0.14	-0.57	0.15	ns	0.28	0.24	-0.28	0.25	<0.001	1.45	0.33	0.85	0.32	ns
	RVIP 2	0.79	0.24	0.10	0.24	<0.001	-0.43	0.14	-0.49	0.14	ns	0.36	0.25	-0.38	0.26	<0.001	1.44	0.32	0.94	0.30	<0.001
	3s	0.62	0.27	0.49	0.28	ns	-0.29	0.10	-0.39	0.11	ns	0.33	0.26	0.10	0.26	ns	1.05	0.33	0.61	0.32	ns
	7s	0.68	0.32	0.59	0.33	ns	-0.33	0.12	-0.39	0.12	ns	0.35	0.32	0.20	0.33	ns	1.16	0.36	0.66	0.38	ns
	RVIP 1	0.90	0.29	0.33	0.30	<0.001	-0.48	0.11	-0.47	0.12	ns	0.42	0.31	-0.14	0.31	<0.001	1.66	0.31	0.90	0.32	<0.001
	RVIP 2	0.88	0.29	0.24	0.30	<0.001	-0.50	0.12	-0.54	0.12	ns	0.38	0.29	-0.30	0.30	<0.001	1.67	0.34	1.00	0.30	<0.001
DAY 56																					
Resting baseline		23.47	1.35	25.40	1.32		12.42	0.66	13.35	0.64		35.79	1.82	38.90	1.77		64.89	1.13	65.15	1.11	
Task epoch (change from resting baseline data)	**3s**	0.12	0.14	-0.04	0.14	ns	0.04	0.07	-0.09	0.07	ns	0.16	0.15	-0.13	0.15	ns	0.07	0.19	0.07	0.17	ns
	7s	0.27	0.19	0.12	0.19	ns	-0.09	0.09	-0.30	0.09	0.001	0.19	0.17	-0.19	0.17	0.007	0.51	0.27	0.55	0.25	ns
	RVIP 1	0.38	0.15	-0.20	0.15	<0.001	-0.19	0.09	-0.20	0.09	ns	0.19	0.14	-0.40	0.14	<0.001	0.29	0.27	0.10	0.22	0.023
	RVIP 2	0.43	0.19	-0.24	0.19	<0.001	-0.25	0.09	-0.18	0.09	ns	0.17	0.19	-0.41	0.19	<0.001	0.31	0.29	0.01	0.24	<0.001
	3s	0.40	0.24	-0.10	0.25	<0.001	-0.22	0.11	-0.24	0.11	ns	0.19	0.22	-0.33	0.23	<0.001	0.67	0.32	0.18	0.31	ns
	7s	0.42	0.25	-0.08	0.25	<0.001	-0.27	0.12	-0.35	0.12	ns	0.15	0.23	-0.43	0.23	<0.001	0.80	0.31	0.45	0.32	ns
	RVIP 1	0.53	0.25	-0.14	0.25	<0.001	-0.30	0.12	-0.29	0.12	ns	0.23	0.20	-0.43	0.21	<0.001	1.04	0.34	0.31	0.33	0.003
	RVIP 2	0.58	0.25	-0.15	0.25	<0.001	-0.32	0.11	-0.28	0.11	ns	0.25	0.23	-0.43	0.23	<0.001	0.79	0.33	0.26	0.31	<0.001
	3s	0.46	0.26	-0.03	0.27	<0.001	-0.21	0.11	-0.22	0.12	ns	0.24	0.23	-0.25	0.24	<0.001	0.94	0.34	0.28	0.33	ns
	7s	0.51	0.31	0.03	0.32	<0.001	-0.23	0.14	-0.27	0.14	ns	0.28	0.26	-0.23	0.27	<0.001	1.03	0.37	0.40	0.39	ns
	RVIP 1	0.61	0.25	-0.09	0.26	<0.001	-0.30	0.12	-0.21	0.12	ns	0.31	0.23	-0.30	0.24	<0.001	0.99	0.32	0.25	0.33	<0.001
	RVIP 2	0.70	0.28	-0.10	0.29	<0.001	-0.30	0.11	-0.24	0.12	ns	0.40	0.30	-0.35	0.30	<0.001	1.03	0.35	0.29	0.31	<0.001

Table S11. Data for the Cognitive Demand Battery outcomes during the qNIRS assessment on Day 1 (all mean plus SEM). Showing raw data for the three pre-dose Day 1 baseline repetitions of the battery (undertaken as part of the cognitive assessment) and the three repetitions of the Cognitive Demand Battery during the post-dose qNIRS assessment.

			Assessment												
			Day 1 Baseline (unadjusted)						2 hours post-dose on Day 1 (change from baseline)						
			Repetition 1		Repetition 2		Repetition 3		Repetition 1		Repetition 2		Repetition 3	
Mental Fatigue (mm)	pl	22	47.23	4.25	49.00	4.69	57.14	5.31	9.36	4.70	10.68	4.17	3.14	4.53
	ZA	20	55.85	4.09	62.00	4.41	67.60	4.20	3.10	4.93	0.95	4.38	-5.15	4.75
RVIP % correct	pl	22	57.95	4.40	55.11	4.26	53.18	4.75	-1.82	2.77	-0.23	3.26	1.02	3.17
	ZA	19	60.00	3.94	59.74	3.74	60.26	3.18	4.47	2.98	0.66	3.51	-1.18	3.41
RVIP RT msec	pl	22	493.3	11.5	487.7	12.3	492.2	11.7	-25.6	18.5	-22.2	18.9	-25.9	17.3
	ZA	19	507.8	9.0	513.9	9.6	523.1	10.5	-5.6	19.9	-5.9	20.3	-16.2	18.6
RVIP FA No.	pl	22	2.41	0.51	1.45	0.41	1.45	0.28	-1.68	0.47	-0.59	0.40	-0.05	0.46
	ZA	19	2.58	0.67	3.05	0.51	2.11	0.40	-0.58	0.51	-1.84	0.43	-0.95	0.50
Serial 3 Correct No.	pl	21	33.05	2.52	35.00	2.62	35.52	2.05	4.14	1.52	4.05	0.91	2.71	1.46
	ZA	20	36.95	3.47	39.10	3.38	38.70	3.38	2.90	1.56	0.80	0.94	1.55	1.50
Serial 3 Error No.	pl	21	1.38	0.36	2.19	0.48	1.76	0.45	0.43	0.63	-0.62	0.61	0.81	0.59
	ZA	20	2.00	0.48	2.30	0.43	3.20	0.59	0.50	0.65	-0.05	0.62	-1.15	0.60
Serial 3 Total No.	pl	21	34.43	2.57	37.19	2.56	37.29	2.12	4.57	1.42	3.43	0.82	3.52	1.30
	ZA	20	38.95	3.32	41.40	3.27	41.90	3.35	3.40	1.45	0.75	0.84	0.40	1.33
Serial 7 Correct No.	pl	21	20.62	2.13	22.76	2.36	21.48	2.19	3.38	1.19	1.86	0.90	2.62	1.30
	ZA	20	22.35	2.34	23.90	2.59	21.75	2.48	4.15	1.22	3.30	0.92	3.60	1.33
Serial 7 Error No.	pl	21	2.14	0.32	2.05	0.38	2.38	0.49	0.19	0.56	0.48	0.48	0.10	0.64
	ZA	20	3.00	0.58	2.85	0.36	4.15	0.82	-0.45	0.58	-0.25	0.50	-1.15	0.66
Serial 7 Total No.	pl	21	22.76	2.07	24.81	2.38	23.86	2.15	3.57	0.98	2.33	0.87	2.71	1.11
	ZA	20	25.35	2.15	26.75	2.49	25.90	2.20	3.70	1.01	3.05	0.89	2.45	1.14

Table S12. Data for the Cognitive Demand Battery outcomes during the qNIRS assessment on Day 56 (all mean plus SEM). Showing raw data for the three pre-dose Day 1 baseline repetitions of the battery (undertaken as part of the cognitive assessment) and the three repetitions of the Cognitive Demand Battery during the post-dose qNIRS assessment on Day 56.

			Assessment									
			Day 1 Baseline (unadjusted)						**2 hours post-dose on Day 1** (change from baseline)			
			Repetition 1		*Repetition 2*		*Repetition 3*		*Repetition 1*		*Repetition 2*		*Repetition 3*
Mental Fatigue (mm)	pl	21	45.76	*4.18*	46.76	*4.33*	55.14	*5.16*	4.67	*4.17*	5.10	*4.11*	-0.24	*5.36*
	ZA	19	55.26	*4.27*	61.42	*4.61*	67.05	*4.39*	0.58	*4.38*	0.58	*4.32*	-2.05	*5.63*
RVIP % correct	pl	21	59.17	*4.44*	55.71	*4.43*	53.33	*4.97*	1.55	*3.89*	1.19	*3.33*	-0.48	*3.53*
	ZA	18	59.31	*4.10*	60.14	*3.93*	60.42	*3.35*	6.67	*4.20*	6.11	*3.59*	0.14	*3.82*
RVIP RT msec	pl	21	492.4	*12.0*	486.4	*12.8*	492.2	*12.3*	-9.6	*9.9*	0.0	*7.3*	1.1	*8.9*
	ZA	18	507.2	*9.5*	510.2	*9.4*	520.6	*10.8*	-2.2	*10.7*	-8.4	*7.9*	-18.9	*9.6*
RVIP FA No.	pl	21	2.00	*0.32*	1.19	*0.33*	1.43	*0.29*	-1.29	*0.51*	-0.43	*0.46*	-0.48	*0.35*
	ZA	18	2.72	*0.69*	3.22	*0.51*	2.22	*0.41*	-1.78	*0.55*	-1.89	*0.50*	-0.61	*0.38*
Serial 3 Correct No.	pl	20	33.60	*2.58*	35.40	*2.72*	36.05	*2.08*	5.75	*1.39*	5.15	*1.15*	4.85	*1.62*
	ZA	19	37.00	*3.65*	39.53	*3.53*	38.84	*3.56*	5.79	*1.43*	3.90	*1.18*	4.53	*1.66*
Serial 3 Error No.	pl	20	1.45	*0.37*	2.30	*0.49*	1.75	*0.48*	0.85	*0.71*	-0.30	*0.61*	-0.30	*0.53*
	ZA	19	2.11	*0.49*	2.32	*0.45*	3.32	*0.61*	0.68	*0.73*	0.05	*0.63*	-1.05	*0.55*
Serial 3 Total No.	pl	20	35.05	*2.62*	37.70	*2.64*	37.80	*2.16*	6.60	*1.29*	4.85	*1.21*	4.55	*1.68*
	ZA	19	39.11	*3.49*	41.84	*3.41*	42.16	*3.52*	6.47	*1.33*	3.95	*1.24*	3.47	*1.72*
Serial 7 Correct No.	pl	20	21.25	*2.14*	23.30	*2.42*	21.85	*2.27*	6.75	*1.23*	4.60	*0.99*	5.30	*1.38*
	ZA	19	22.37	*2.47*	24.16	*2.72*	21.74	*2.62*	6.79	*1.26*	4.95	*1.02*	4.95	*1.42*
Serial 7 Error No.	pl	20	2.20	*0.33*	2.05	*0.40*	2.50	*0.49*	-0.70	*0.57*	-0.10	*0.55*	-0.85	*0.72*
	ZA	19	3.16	*0.59*	2.84	*0.38*	4.32	*0.85*	-0.26	*0.59*	0.00	*0.56*	-0.63	*0.74*
Serial 7 Total No.	pl	20	23.45	*2.06*	25.35	*2.44*	24.35	*2.20*	6.05	*0.96*	4.50	*1.00*	4.45	*1.12*
	ZA	19	25.53	*2.26*	27.00	*2.61*	26.05	*2.31*	6.53	*0.99*	4.95	*1.03*	4.32	*1.15*