Supplementary Information

1. Supplementary method:

1.1 Participants Exclusion Criteria

1) Has a history of a psychiatric disorder such as schizophrenia, bipolar disorder, or major depression according to the criteria of the most current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM).
2) Mild depression or history of depression that is stable on treatment with SSRI or SNRI medication at a stable dose is acceptable.
3) History of a seizure disorder.
4) Has a history or current evidence of long QT syndrome, Fridericia's formula corrected QT (QTcF) interval ≥ 450ms, or torsades de pointes.
5) Has bradycardia (<50 bpm) or tachycardia (>100 bpm) on the ECG at screening.
6) Has uncontrolled Type-1 or Type-2 diabetes. A Subject with HbA1c levels up to 7.5% can be enrolled if the investigator believes the subject's diabetes is under control.
7) Has clinically significant renal or hepatic impairment.
8) Has any clinically significant abnormal laboratory values. Subjects with liver function tests (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) greater than twice the upper limit of normal will be excluded.
9) Is at imminent risk of self-harm, based on clinical interview and responses on the C SSRS, or of harm to others in the opinion of the Investigators. Subjects must be excluded if they report suicidal ideation with intent, with or without a plan or method (e.g. positive response to Items 4 or 5 in assessment of suicidal ideation on the C SSRS) in the past 2 months, or suicidal behavior in the past 6 months.
10) Has four or more signal hypo intensities on T2*-weighted gradient recalled echo magnetic resonance sequences that are thought to represent hemosiderin deposits including microhemorrhages and superficial siderosis or evidence of acute or sub-acute micro or microhemorrhage as noted on the MRI scan.
11) Has cancer or has had a malignant tumor within the past year, except patients who underwent potentially curative therapy with no evidence of recurrence. (Patients with stable untreated prostate cancer or skin cancers are not excluded).
12) Alcohol / Substance use disorder, moderate to severe, in the last 5 years according to the most current version DSM.
13) Participation in another clinical trial with an investigational agent and have taken at least one dose of study medication, unless unblinded on placebo, within 60 days prior to the start of screening. (The end of a previous investigational trial is the date the last dose of an investigational agent was taken), or five half-lives of the investigational drug, whichever is greater.
14) Subjects with infection or inflammation of the skin or skin disease at or in proximity to the lumbar puncture site.
15) History of lumbar spine surgery or chronic low back pain (CLBP).
16) Subjects with learning disability or developmental delay.

1.2 Buntanetap Pharmacokinetics

The determination of buntanetap in human plasma was performed using an assay range of 0.100 to 150 ng/mL.

Calibration standard samples were prepared in human plasma (K_2EDTA) from dilutions of the buntanetap stock solutions. The calibration standards samples were prepared at nominal concentrations of 0.100 to 150 ng/mL using their respective spiking solutions.

Quality control samples were prepared, in human plasma (K_2EDTA) at nominal concentrations of 0.300, 30.0, 60.0 and 120 ng/mL, using their respective spiking solutions.

For the analysis of human plasma samples, aliquots of calibration standards, quality control samples and study samples were processed by performing a protein precipitation extraction procedure under wet-ice conditions and were then injected into the LC-MS/MS system.

The Shimadzu LC system and Sciex API 4000 mass spectrometer were equipped with an analytical column Kinetex Biphenyl 100 Å (50 X 2.1 mm, 2.6 µm i.d.) to monitor the peak of interest. The mobile phase consisted of a binary flow elution of 0.1% formic acid in water and acetonitrile with a flow rate of 0.400 mL/min.

The quantitation of buntanetap was performed using peak area ratios. A 1/concentration weighted linear regression was used to determine the concentrations of buntanetap in human plasma.

2. Demographic and Baseline Characteristics of AD and PD patients

Supplementary Table 1-1: Summary of Demographics and Baseline Characteristics of PD Patients

Classification	Statistic	Placebo (N=5)	Posiphen 80mg QD (N=10)	Posiphen 5mg QD (N=12)	Posiphen 10mg QD (N=10)	Posiphen 20mg QD (N=11)	Posiphen 40mg QD (N=10)	Total (N=58)
Age (years)	n	5	10	12	10	11	10	58
	Mean	75.4	65.0	67.2	62.0	69.8	62.5	66.3
	SD	3.13	9.31	6.94	9.93	10.93	6.74	9.12
	Median	76	66.5	67.5	59	69	63	67.5
	Q1	76	54	62	55	61	59	59
	Q3	77	73	72.5	72	81	65	74
	Min	70	51	55	49	50	52	49
	Max	78	77	77	77	84	74	84
Sex n(%)	Male	3 (60.0%)	8 (80.0%)	10 (83.3%)	7 (70.0%)	8 (72.7%)	8 (80.0%)	44 (75.9%)
	Female	2 (40.0%)	2 (20.0%)	2 (16.7%)	3 (30.0%)	3 (27.3%)	2 (20.0%)	14 (24.1%)
Ethnicityn(%)	HISPANIC OR LATINO	2 (40.0%)	0 (0.0%)	3 (25.0%)	2 (20.0%)	5 (45.5%)	0 (0.0%)	12 (20.7%)
	NOT HISPANIC OR LATINO	3 (60.0%)	10 (100.0%)	9 (75.0%)	8 (80.0%)	6 (54.5%)	10 (100.0%)	46 (79.3%)
Race n(%)	WHITE	5 (100.0%)	10 (100.0%)	12 (100.0%)	10 (100.0%)	9 (81.8%)	10 (100.0%)	56 (96.6%)
	BLACK OR AFRICAN AMERICAN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	1 (1.7%)
	ASIAN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	1 (1.7%)
Height (cm)	n	5	10	12	10	11	10	58
	Mean	167.5	176.0	175.6	173.4	168.3	177.5	173.5
	SD	13.46	13.10	11.64	9.32	11.81	11.35	11.74
	Median	172	176.9	174.13	174.4	170.5	181.44	174.63
	Q1	157.5	168.5	168	167.6	155	163	166
	Q3	175.3	186.7	186.75	178	180	185	182.9
	Min	150	147.5	154	160	151	162.6	147.5
	Max	182.9	191	191	191	184	194	194

Classification	Statistic	Placebo (N=5)	Posiphen 80mg QD (N=10)	Posiphen 5mg QD (N=12)	Posiphen 10mg QD (N=10)	Posiphen 20mg QD (N=11)	Posiphen 40mg QD (N=10)	Total (N=58)
Weight (kg)	n	5	10	12	10	11	10	58
	Mean	88.0	114.9	143.0	116.7	105.8	107.2	115.7
	SD	21.45	71.48	62.85	59.27	33.53	34.50	52.89
	Median	84.7	87.75	146	95.75	109.4	92.15	96.15
	Q1	77.5	77.5	92.15	69.9	79	86.2	79
	Q3	86.4	106.7	185.95	158	132.8	119	143
	Min	67.5	63.7	56.4	62.1	56.9	76	56.4
	Max	124	292.5	260	220	150.7	177	292.5
BMI (kg/m^2)	n	5	10	12	10	11	10	58
	Mean	26.6	28.6	26.9	28.1	29.6	28.3	28.1
	SD	4.36	5.19	3.84	5.07	7.80	3.82	5.15
	Median	25.22	27.335	25.77	27.4	26.27	28.21	27.16
	Q1	25.04	24.61	24.28	23.52	24.66	25.59	24.66
	Q3	25.83	30.61	30.59	33.2	37.63	30.38	30.96
	Min	22.82	23.12	19.97	21.51	20.06	21.7	19.97
	Max	34.14	38.59	32.5	34.38	44.51	34.77	44.51

Supplementary Table 1- 2: Summary of Demographics and Baseline Characteristics of AD Patients

Classification	Statistic	Placebo (N=6)	Posiphen 80mg QD (N=10)	Total (N=16)
Age (years)	n	6	10	16
	Mean	68.0	72.8	71.0
	SD	6.87	6.34	6.75
	Median	65.5	73	72
	Q1	63	72	65
	Q3	75	77	76.5
	Min	61	60	60
	Max	78	81	81
Sex n(%)	Male	3 (50.0%)	2 (20.0%)	5 (31.3%)
	Female	3 (50.0%)	8 (80.0%)	11 (68.8%)
Ethnicityn(%)	HISPANIC OR LATINO	4 (66.7%)	5 (50.0%)	9 (56.3%)
	NOT HISPANIC OR LATINO	2 (33.3%)	5 (50.0%)	7 (43.8%)
Race n(%)	WHITE	4 (66.7%)	8 (80.0%)	12 (75.0%)
	BLACK OR AFRICAN AMERICAN	1 (16.7%)	0 (0.0%)	1 (6.3%)
	ASIAN	1 (16.7%)	1 (10.0%)	2 (12.5%)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0 (0.0%)	1 (10.0%)	1 (6.3%)
Height (cm)	n	6	10	16
	Mean	163.4	164.7	164.2
	SD	8.97	9.30	8.89
	Median	163.8	162.5	162.5
	Q1	157	157	157
	Q3	170	171	170.5
	Min	151	154	151
	Max	175	183	183

Classification	Statistic	Placebo (N=6)	Posiphen 80mg QD (N=10)	Total (N=16)
Weight (kg)	n	6	10	16
	Mean	68.1	71.7	70.4
	SD	6.69	12.56	10.63
	Median	67	68.65	67
	Q1	62.1	63.3	62.7
	Q3	73.4	85	75.8
	Min	60.8	57.2	57.2
	Max	78.2	89.8	89.8
BMI (kg/m^2)	n	6	10	16
	Mean	25.6	26.4	26.1
	SD	3.65	4.13	3.85
	Median	25.065	25.71	25.42
	Q1	23.5	23.2	23.35
	Q3	26.56	28.34	27.865
	Min	21.46	21.23	21.23
	Max	32.19	35.07	35.07

3. Safety Data

Supplementary Table 2-1: Summary of all treatment-emergent adverse events in PD patients

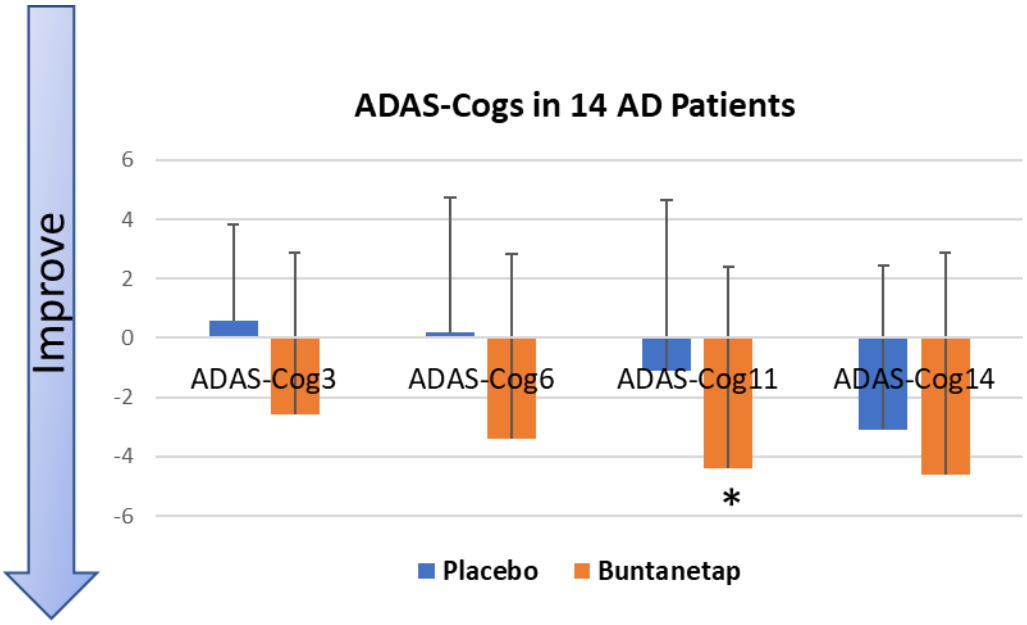
	Placebo (N=5)	Posiphen 80mg QD (N=10)	Posiphen 5mg QD (N=12)	Posiphen 10mg QD (N=10)	Posiphen 20mg QD (N=11)	Posiphen 40mg QD (N=10)	Total (N=58)
Subjects with any AEs	3 (60.0%)	3 (30.0%)	1 (8.3%)	7 (70.0%)	5 (45.5%)	5 (50.0%)	24 (41.4%)
Number of AEs	5	3	5	24	12	8	57
Subjects with serious TEAEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment Emergent Adverse Events (TEAEs)	3 (60.0%)	3 (30.0%)	1 (8.3%)	6 (60.0%)	4 (36.4%)	5 (50.0%)	22 (37.9%)
Subjects with TEAEs that led to Drug Interrupted	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
Subjects with TEAEs that led to Drug Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects with TEAEs that suspected to be drug related	1 (20.0%)	0 (0.0%)	0 (0.0%)	2 (20.0%)	1 (9.1%)	2 (20.0%)	6 (10.3%)
Subjects with TEAEs that resulted in death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects with TEAEs that related to Study Procedure	2 (40.0%)	1 (10.0%)	1 (8.3%)	6 (60.0%)	3 (27.3%)	3 (30.0%)	16 (27.6%)
CTCAE Grade 1	3 (60.0%)	3 (30.0%)	1 (8.3%)	5 (50.0%)	3 (27.3%)	3 (30.0%)	18 (31.0%)
CTCAE Grade 2	0 (0.0%)	0 (0.0%)	1 (8.3%)	1 (10.0%)	1 (9.1%)	3 (30.0%)	6 (10.3%)
CTCAE Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)

Supplementary Table 2-2: Summary of all treatment-emergent adverse events in AD patients

	Placebo (N=6)	Posiphen 80mg QD (N=10)	Total (N=16)
Subjects with any AEs	3 (50.0%)	5 (50.0%)	8 (50.0%)
Number of AEs	4	8	12
Subjects with serious TEAEs	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment Emergent Adverse Events (TEAEs)	3 (50.0%)	5 (50.0%)	8 (50.0%)
Subjects with TEAEs that led to Drug Interrupted	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects with TEAEs that led to Drug Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects with TEAEs that suspected to be drug related	0 (0.0%)	1 (10.0%)	1 (6.3%)
Subjects with TEAEs that resulted in death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects with TEAEs that related to Study Procedure	3 (50.0%)	4 (40.0%)	7 (43.8%)
CTCAE Grade 1	3 (50.0%)	4 (40.0%)	7 (43.8%)
CTCAE Grade 2	0 (0.0%)	1 (10.0%)	1 (6.3%)

4.Supplementary Figures

Supplementary Figure 1: Multiple ADAS-Cogs were measured in AD patients. Buntanetap treated group showed a trend of improvement in ADAS-Cog 3, 6, 14 as well as a significant improvement in ADAS-Cog11 comparing to its baseline.



Supplementary Figure 2: MMSE, CDR Sum of Boxes were measured in AD patients. There is no statistically significant difference between placebo and buntanetap treated patients.