Study No: P02-31UK	
Title: Examination of Bupropion and Ethanol, Alone and in Combination, on Human Performance Tests, Subjective Rating Scales, EEG and Autonomic Responses	
Rationale: Given the ubiquitous use of alcohol by depressed individuals and the prevalence of depression in subjects with alcohol abuse or alcoholism, concern over an antidepressant-alcohol interaction is a significant public health consideration. The interaction of therapeutic dose levels of tricyclic antidepressants with alcohol is a well-known phenomenon, producing enhanced sedation or even coma. Death may occur at higher doses of tricyclics when taken in combination with non-lethal amounts of alcohol. Interestingly, even outpatient doses of amitryptyline given in conjunction with low to moderate amounts of alcohol impair psychomotor performance and driving skills. Therefore, this study was conducted to determine whether bupropion (BUP), like the tricyclic antidepressants, has a propensity to potentiate the central nervous system (CNS) effects of alcohol. The effects of acute oral dose of BUP (100mg) and alcohol (16mL and 32mL of 100% alcohol), given singly and in combination, were evaluated on psychomotor performance tests and subjective ratings of healthy volunteers.	
Phase: I	
Study Period: Study report issued on 3/18/82	
Study Design: A double-blind, double-dummy, 6-way, Latin Square cross-over, single-dose comparison study.	
Centres: A single centre in the United Kingdom.	
Indication: None	
Treatment: The following treatments were administered in a randomised, cross-over fashion in weekly intervals: BUP hydrochloride (HCl) 100mg and placebo (PBO)-alcohol BUP HCl 100mg and alcohol 16mL (A16) Alcohol 32mL (A32) and PBO-BUP HCl Alcohol 16mL (A16)and PBO-BUP HCl PBO-BUP HCl and PBO-alcohol BUP HCl 100mg and alcohol 32mL (A32)	
Objectives: The primary objectives of the study was to determine if the combination of BUP and alcohol produces effects different from BUP alone or alcohol alone on the following measures: Behavioural performance (vigilance, reaction time, short-term memory, finger tapping) Autonomic functioning (heart rate [HR], blood pressure [BP], pupil size) Electroencephalogram (EEG; frequency band analysis) Mood (visual analog scale) Side effects	
Statistical Methods: All measured variables were analysed as raw scores by analysis of variance (ANOVA). Main effects of treatments (and also subjects and occasions of testing differences) were sought. Visual analog scale scores from alert/drowsy, clear-headed/muzzy, quick-witted/mentally slow, and attentive/dreamy were combined to give a mental sedation score. Fisher's missing plot technique was used to account for missing data. All analyses were performed on the total population. No formal sample size calculations were performed.	
Study Population: Healthy male and female volunteers. Subjects were interviewed regarding past illnesses and had full physical and clinical laboratory examinations. All female subjects had a pregnancy test prior to the study and during each week of the study. Subjects were chosen who did not drink >3 pints beer or >3 double measures of "spirits" per day.	

Number of Subjects:	**Total**
Planned, N	12
Dosed, N	12
Completed, n (%)	12 (100)
Total Number Subjects Withdrawn, n (%)	0
Withdrawn Due to Adverse Events (AEs), n (%)	0
Withdrawn Due to Lack of Efficacy, n (%)	0
Withdrawn For Other Reasons, n (%)	0
Demographics:	**Total**
N (Total)	12

Females:Males, n:n			6:6				

			Males		**Females**		
Mean Age in Years (Range)			26 (20, 31)		22 (20, 25)		
Mean Weight in Kg (Range)			72 (57, 94)		58 (48, 65)		
Race, n (%)			Not available				

Study Endpoints:

Performance Test Results (Mean Scores[a])	**Treatment Means**						**SEM**
Auditory Vigilance (Correct Detections/15min)	**A32**	**A16**	**PBO**	**BUP/A32**	**BUP/A16**	**BUP**	±1.09
	4.35[a]	4.69[ab]	4.73[ab]	5.08[b]	5.18[b]	5.35[b]	
Tapping Rate (taps/min)	**BUP/A32**	**BUP**	**A16**	**PBO**	**BUP/A16**	**A32**	±3.49
	359[c]	359[c]	361[c]	364[c]	367[c]	371[c]	
Auditory Reaction Time (ms)	**BUP**	**A32**	**A16**	**PBO**	**BUP/A16**	**BUP/A32**	±6.08
	278[d]	279[d]	280[d]	284[d]	284[d]	289[d]	
Short-term Memory (Total Errors)	**BUP/A16**	**A16**	**PBO**	**BUP**	**BUP/A32**	**A32**	±3.37
	54.0[e]	54.2[e]	58.8[e]	59.9[e]	63.4[e]	63.4[e]	

A32=32mL alcohol + placebo BUP; A16=16mL alcohol + placebo BUP; BUP=BUP 100mg + placebo alcohol;
BUP/A16= BUP 100mg + 16mL alcohol; BUP/A32= BUP 100mg + 32mL alcohol.
Mean values (± standard error [SE, SEM] are presented for 12 subjects after each of the 6 treatments. Duncan's Multiple Range Test was used to compare mean scores. Means are ranked in ascending order.
a-e : means in each test with a common letter do not differ significantly (p > 0.05). Means in each test with a different letter are significantly different (p ≤ 0.05).

Autonomic Measures (Mean Values)	**PBO**	**BUP**	**A16**	**A32**	**BUP/A16**	**BUP/A32**	**Significant Difference**
Heart Rate (beats/min)							
Pre-treatment	65.3	63.9	68.7	63.1	65.0	63.7	None
3h 15min post drug	61.8	62.8	63.8	64.2	63.0	69.8	BUP/A32 vs all other treatments
6h 30min post drug	69.8	71.7	71.2	72.2	73.3	74.8	None
Pupil Diameter (mm, mean of both pupils)							
Pre-treatment	6.00	5.77	6.41	6.15	6.09	6.03	None
3h 15min post drug	6.23	6.25	6.40	6.08	6.09	6.33	BUP vs A16, BUP/A16 PBO vs A16, BUP/A16
6h 30min post drug	6.01	6.39	6.23	6.24	6.28	6.46	None

EEG Analysis (Significance of Differences)

Conditions	**Treatments**						
Eyes Open							
3hr post drug	4.0-7.5Hz	BUP/A16[a]	BUP[a]	A16[a]	BUP/A32[a]	PBO[ab]	A32[b]
Eyes Closed							
3hr post drug	2.3-4.0Hz	BUP/A16[c]	BUP[cd]	BUP/A32[cd]	A16[cd]	PBO[d]	A32[d]
	4.0-7.5 Hz	BUP/A32[e]	BUP[e]	BUP/A16[e]	A16[ef]	PBO[ef]	A32[f]

Mean EEG energy in the 4 filter bands of 12 subjects after 6 treatments at different times with eyes open or closed was examined. Duncan's Multiple Range Test was used to compare differences in treatments. Means are ranked in ascending order.
a-f : means in each test with a common letter do not differ significantly (p > 0.05). Means in each test with a different letter are significantly different (p ≤ 0.05).

Visual Analogue Scale (Measure of Subjective Effects)

Time	**Subjective Feeling**	**Treatment Means**						**SEM**
2hr 40min post drug	Clear-headed/ Muzzy	**BUP**	**PBO**	**BUP/A16**	**A16**	**BUP/A32**	**A32**	±6.72
		47.3[a]	48.3[a]	54.4[ab]	60.6[ab]	64.0[b]	67.3[b]	
	Quick-witted/ Mentally Slow	**BUP**	**BUP/A16**	**PBO**	**BUP/A32**	**A16**	**A32**	±5.74
		48.6[c]	48.7[c]	49.5[c]	58.9[cd]	59.5[cd]	62.8[d]	
	Completely Sober/ Extremely Drunk	**BUP**	**PBO**	**A16**	**BUP/A16**	**BUP/A32**	**A32**	±4.77
		1.50[e]	2.67[e]	12.6[f]	16.1[f]	40.8[g]	42.6[g]	

5hr post drug	Clear-headed/ Muzzy	**PBO**	**BUP/A16**	**BUP**	**A16**	**BUP/A32**	**A32**	±3.78
		45.8 [h]	48.5 [hi]	55.6 [hij]	58.2 [ij]	59.5 [ij]	61.4 [j]	
	Quick-witted/ Mentally Slow	**BUP/A16**	**PBO**	**BUP/A32**	**BUP**	**A16**	**A32**	
		46.0 [k]	46.2 [k]	53.3 [kl]	53.5 [kl]	57.3 [l]	58.8 [l]	
	Attentive/ Dreamy	**BUP/A16**	**PBO**	**BUP**	**BUP/A32**	**A32**	**A16**	±3.26
		50.1 [m]	50.3 [m]	54.9 [mn]	57.0 [mn]	61.0 [no]	68.3 [o]	
	Completely Sober/ Extremely Drunk	**PBO**	**BUP**	**A16**	**BUP/A16**	**BUP/A32**	**A32**	±1.48
		0.67 [p]	0.75 [p]	1.08 [p]	1.25 [p]	6.50 [q]	7.08 [q]	
2hr 40min post drug	Mental Sedation	**BUP**	**PBO**	**BUP/A16**	**BUP/A32**	**A16**	**A32**	±4.00
		49.3 [r]	50.0 [r]	54.2 [rs]	58.6 [rs]	60.1 [rs]	65.4 [s]	
5hr post drug	Mental Sedation	**PBO**	**BUP/A16**	**BUP**	**BUP/A32**	**A32**	**A16**	±2.72
		48.8 [t]	49.1 [t]	55.5 [tu]	56.9 [tu]	60.3 [u]	61.3 [u]	

Duncan's Multiple Range Test was used to compare differences in treatments. Means are ranked in ascending order.

a-u : means in each test with a common letter do not differ significantly (p > 0.05). Means in each test with a different letter are significantly different (p ≤ 0.05).

Safety Results: Side effects were assessed via a checklist. There are no Adverse Events or SAE listed in study report or GSK database.

	Total N=12
Most Frequent Adverse Events	n (%)
Number of Subjects With AEs	Not available

	Total N=12
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]	n (%)
Number of Subjects With SAEs (Fatal And Non-fatal)	Not available

Conclusion:
See publication below

Publications:
Hamilton, MJ, Bush, MS and Peck AW. The effect of bupropion, a new antidepressant drug, and alcohol and their interaction in man. Eur J Clin Pharmacol 27:75-80, 1984

Date Updated: 17-Oct-2005