The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: Paracetamol and Caffeine

Study Number: RH01361

Title: Effects of Two Doses of a Common Cold Treatment on Cognitive Function

Rationale: Common cold is commonly associated with reduction in alertness and lower level of performance. The aim of this study was to assess the change in alertness level in people suffering from the common cold following administration of 1000 mg paracetamol and 130 mg caffeine combination tablet. Auditory and Visual attention of the subjects was assessed using validated cognitive tests like Rapid Visual Information Processing (RVIP), Sustained Attention Task (SAT) and Divided Attention Task (DAT).

Phase: III

Study Period: 7 Nov 2011 – 31 Oct 2012

Study Design: This was a double-blind, randomized, placebo-controlled, single centre study. The study consisted of a Screening Period and a Treatment Period.

Centres: Single Centre in UK

Indication: Common Cold

Treatment: Tablets were dissolved in 200 mL of water and administered orally.

1. **Treatment A:** Two tablets each containing paracetamol (500 mg) and caffeine (65 mg) (Total Dose: 1000 mg/130 mg)
2. **Treatment B:** Two Paracetamol tablets (500 mg each) (Total Dose: 1000 mg)
3. **Treatment C:** One tablet containing paracetamol (500 mg) and caffeine (65 mg) (Total Dose: 500 mg/65 mg)
4. **Treatment D:** One paracetamol tablet (500 mg)

Objectives: The primary objective of the study was

1. To assess the change in alertness level in people suffering from the common cold, 60 minutes following paracetamol 1000 mg and caffeine 130 mg compared to paracetamol 1000 mg.
2. To assess the change in alertness level in people suffering from the common cold, 60 minutes following paracetamol 500 mg and caffeine 65 mg compared to paracetamol 500 mg.

Primary Efficacy Variable: The primary outcome of the study was efficacy. Primary endpoints included:

1. Number of accurate responses to RVIP Cognitive test at 60 minutes

Secondary Outcome/Efficacy Variable(s):

1. Number of accurate responses to RVIP Cognitive test at 120 minutes
2. Time of accurate responses to RVIP Cognitive Task
3. Number of inaccurate and missed responses to RVIP Cognitive Task
4. Number of accurate responses to SAT Cognitive test
5. Time of accurate responses to SAT Cognitive Task
6. Number of incorrect and missed responses to SAT Cognitive test
7. Number of accurate responses to DAT Cognitive test
8. Time of accurate responses to DAT Cognitive test
9. Number of incorrect and missed responses to DAT Cognitive test

Statistical Methods:

For the number of accurate responses to the RVIP task and the mean time of accurate responses to the SAT and DAT, and for each grouping of questions from the mood evaluation questionnaire, an analysis of covariance (ANCOVA) on the change from baseline to 60 and 120 minutes, was performed. The ANCOVA model included treatment group and season as factors and the corresponding baseline value as a covariate.

For the number of accurate responses to the RVIP task, the treatment x baseline interaction was significant ($p<0.1$)..A 3-level categorical variable was created, and treatment effect calculated within each of the 3 levels of baseline value.

For the mean time of accurate responses to the RVIP task, and the number of accurate responses to the sustained auditory task and sustained divided attention task, the assumptions of normality were violated. These variables were analysed using the Wilcoxon rank sum test, and 95% confidence intervals (CI) calculated using the Hodges- Lehmann method. The number of inaccurate responses and number of missed responses to each of the cognitive function tests were summarised by treatment group using descriptive statistics.

The Intent-To-Treat (ITT) population was the primary population for efficacy analysis, and included all subjects who were randomised, received study treatment and had at least one post-baseline efficacy evaluation.

The Safety population included all subjects who were randomised and received study treatment.

Study Population:
Subjects in good general health, aged 18 years of age or above, willing to participate, and presented symptoms of common cold of no more than 96 hours duration. Symptoms of common cold being self-rating of at least "2" for malaise at the screening visit with at least 4 other symptoms associated with the common cold.

	A	**B**	**C**	**D**
Number of Subjects:				
Planned, N	45	45	75	75
Randomised, N	45	45	75	75
Completed, n (%)	45 (100%)	45 (100%)	75 (100%)	75 (100%)
Total Number Subjects Withdrawn, N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Demographics	**A**	**B**	**C**	**D**
N (Safety Population)	46[#]	45	74	75
N (ITT)	45	45	75	75
Females: Males	31: 15	28: 17	47: 27	48: 27
Mean Age, years (SD)	20.0 (1.56)	20.0 (1.74)	20.6 (4.19)	20.2 (2.80)
Race, n (%)				
White	40 (87.00)	43 (95.60)	71 (95.90)	70 (93.30)
Black	3 (6.50)	1 (2.20)	2 (2.70)	2 (2.70)
Asian	3 (6.50)	1 (2.20)	1 (1.40)	3 (4.00)

[#]One subject randomized to Treatment C but received Treatment A.

Primary Efficacy Results:

1. Number of accurate responses to RVIP Cognitive test at 60 minutes

	A	**B**	**C**	**D**
Mean Baseline (SE)	23.4 (1.51)	22.3 (1.46)	21.2 (1.05)	22.7 (1.08)
Change from Baseline (CFB) at 60 minutes, Adjusted Mean (SE)	8.3 (1.12)	4.8 (1.12)	4.5 (0.89)	2.7 (0.88)
Treatment Comparisons				
	Adjusted Mean Difference[1]		**95% CI**	**P Value**
A vs B	3.5		0.4, 6.5	0.0248
C vs D	1.7		-0.6, 4.1	0.1513
A vs C	3.9		1.1, 6.6	

[1] A positive difference favours the first named treatment.
[2] A hierarchical testing procedure is used such that p-values are only presented if the preceding treatment comparison is statistically significant (p<0.05).

Secondary Efficacy Results:

1. ***Number of accurate responses to RVIP Cognitive test at 120 minutes***

	A	**B**	**C**	**D**
CFB at 120 minutes, Adjusted Mean (SE)	7.3 (1.16)	4.4 (1.15)	6.2 (0.91)	3.5 (0.92)
Treatment Comparisons				
	Adjusted Mean Difference[1]		**95% CI**	**P Value**[2]
A vs B	2.9		-0.2, 6.1	0.0696
C vs D	2.7		0.3, 5.2	
A vs C	1.1		-1.7, 3.9	

[1] A positive difference favours the first named treatment.
[2] A hierarchical testing procedure is used such that p-values are only presented if the preceding treatment comparison is statistically significant (p<0.05).

2. ***Time of accurate responses to RVIP Cognitive test (in milliseconds)***

	A	**B**	**C**	**D**
Baseline, Median (Range)	418.6 (177 to 495)	420.7 (1 to 520)	422.9 (183 to 509)	415.3 (268 to 548)
CFB at 60 minutes, Median (Range)	-1.4 (-92 to 102)	2.4 (-113 to 313)	-0.9 (-134 to 119)	-9.9 (-108 to 142)
CFB at 120 minutes, Median (Range)	-10.3 (-62 to 125)	-6.0 (-86 to 71)	-12.5 (-91 to 109)	-14.0 (-144 to 136)
Treatment Comparisons				
60 minutes	**Median Difference**[1]		**95% CI**	**P Value**[2]

A vs B	-1.4		-16.0, 14.4	0.8450
C vs D	9.0		-2.7, 20.5	
A vs C	-0.9		-14.1, 13.1	
120 minutes	**Median Difference[1]**		**95% CI**	**P Value[2]**
A vs B	-4.0		-20.3, 12.3	0.6029
C vs D	4.8		-7.5, 18.0	
A vs C	0.6		-12.0, 12.7	
[1] A negative difference favours the first named treatment. [2] From Wilcoxon Rank Sum Test. A hierarchical testing procedure is used such that p-values are only presented if the preceding treatment comparison is statistically significant (p<0.05).				
3. Number of inaccurate and missed responses to RVIP Cognitive test				
Inaccurate Responses	**A**	**B**	**C**	**D**
Baseline, Mean (SE)	33.6 (4.37)	29.4 (2.47)	32.8 (3.04)	30.2 (1.80)
CFB at 60 minutes, Mean (SE)	-5.7 (3.43)	-2.8 (1.38)	1.4 (1.96)	-2.4 (1.82)
CFB at 120 minutes, Mean (SE)	-4.5 (4.12)	-1.7 (1.78)	-0.8 (1.97)	-3.3 (1.56)
Missed Responses	**A**	**B**	**C**	**D**
Baseline, Mean (SE)	48.6 (1.51)	49.7 (1.46)	50.8 (1.05)	49.3 (1.08)
CFB at 60 minutes, Mean (SE)	-8.1 (1.03)	-4.8 (1.18)	-4.8 (0.83)	-3.1 (0.89)
CFB at 120 minutes, Mean (SE)	-7.6 (1.14)	-4.8 (1.15)	-6.5 (0.80)	--3.5 (0.92)
4. Number of accurate responses to SAT Cognitive test				
	A	**B**	**C**	**D**
Baseline, Median (Range)	46.5 (18 to 49)	45.0 (0 to 50)	45.0 (12 to 50)	45.0 (22 to 50)
CFB at 60 minutes, Median (Range)	1.0 (-4 to 16)	0.5 (-16 to 43)	2.0 (-9 to 33)	0.0 (-28 to 15)
CFB at 120 minutes, Median (Range)	2.0 (-17 to 28)	1.0 (-11 to 42)	1.0 (-6 to 30)	2.0 (-10 to 26)
Treatment Comparisons				
60 minutes	**Median Difference[1]**		**95% CI**	**P Value[2]**
A vs B	1.0		1.0, 2.0	0.2793
C vs D	1.0		0.0, 2.0	
A vs C	0.0		-1.0, 1.0	
120 minutes	**Median Difference[1]**		**95% CI**	**P Value[2]**
A vs B	1.0		-1.0, 3.0	0.3919
C vs D	0.0		-2.0, 1.0	
A vs C	1.0		-1.0, 2.0	
[1] A positive difference favours the first named treatment. [2] A hierarchical testing procedure is used such that p-values are only presented if the preceding treatment comparison is statistically significant (p<0.05).				
5. Time of accurate responses to SAT Cognitive test (in milliseconds)				
	A	**B**	**C**	**D**
Baseline, Mean (SE)	376.7 (4.61)	373.7 (4.37)	373.5 (2.93)	369.4 (3.07)
CFB at 60 minutes, Adjusted Mean (SE)	-16.7 (3.17)	-9.8 (3.17)	-10.8 (2.51)	-12.0 (2.47)
CFB at 120 minutes, Adjusted Mean (SE)	-21.2 (3.48)	-10.4 (3.48)	-18.0 (2.74)	-15.4 (2.72)
Treatment Comparisons				
60 minutes	**Adjusted Mean Difference[1]**		**95% CI**	**P Value[2]**
A vs B	-7.0		-15.6, 1.6	0.1116
C vs D	1.1		-5.5, 7.8	
A vs C	-5.9		-13.6, 1.8	
120 minutes	**Adjusted Mean Difference[1]**		**95% CI**	**P Value[2]**
A vs B	-10.8		-20.3, -1.4	0.0251
C vs D	-2.6		-9.9, 4.7	0.4848
A vs C	-3.2		-11.7, 5.2	
[1] A negative difference favours the first named treatment. [2] A hierarchical testing procedure is used such that p-values are only presented if the preceding treatment comparison is statistically significant (p<0.05).				
6. Number of inaccurate and missed responses to SAT Cognitive test				
Inaccurate Responses	**A**	**B**	**C**	**D**
Baseline, Mean (SE)	13.4 (1.11)	12.8 (1.00)	13.8 (0.91)	12.8 (0.85)

CFB at 60 minutes, Mean (SE)	-4.6 (1.00)	-1.1 (0.87)	-4.2 (0.74)	-1.6 (0.71)
CFB at 120 minutes, Mean (SE)	-4.4 (1.04)	-2.3 (0.98)	-4.3 (0.88)	-2.8 (0.82)
Missed Responses				
Baseline, Mean (SE)	6.5 (0.97)	6.9 (1.25)	6.5 (0.68)	6.0 (0.62)
CFB at 60 minutes, Mean (SE)	-2.7 (0.74)	-1.9 (1.25)	-2.3 (0.70)	-0.8 (0.66)
CFB at 120 minutes, Mean (SE)	-2.8 (1.11)	-2.0 (1.19)	-2.2 (0.64)	-2.4 (0.63)
7. Number of accurate responses to DAT Cognitive test				
	A	**B**	**C**	**D**
Baseline, Median	78.0 (41 to 94)	79.0 (0 to 96)	77.0 (27 to 95)	80.0 (2 to 95)
CFB at 60 minutes, Median	10.0 (-9 to 34)	6.0 (-35 to 66)	8.0 (-9 to 45)	5.5 (-27 to 82)
CFB at 120 minutes, Median	11.0 (-6 to 53)	6.0 (-15 to 88)	9.0 (-23 to 59)	7.0 (-23 to 86)
Treatment Comparisons				
60 minutes	**Median Difference**[1]		**95% CI**	**P Value**[2]
A vs B	4.0		0.0, 7.0	0.0444
C vs D	3.0		1.0, 6.0	0.0120
A vs C	1.0		-2.0, 5.0	0.4727
120 minutes	**Median Difference**[1]		**95% CI**	**P Value**[2]
A vs B	5.0		1.0, 8.0	0.0101
C vs D	3.0		-1.0, 6.0	0.1075
A vs C	2.0		-1.0, 5.0	
[1] A positive difference favours the first named treatment. [2] A hierarchical testing procedure is used such that p-values are only presented if the preceding treatment comparison is statistically significant (p<0.05).				
8. Time of accurate responses to DAT Cognitive test (in milliseconds)				
	A	**B**	**C**	**D**
Baseline, Mean (SE)	366.7 (3.20)	366.9 (3.07)	364.2 (2.56)	367.0 (2.77)
CFB at 60 minutes, Adjusted Mean (SE)	-3.0 (2.94)	1.5 (2.94)	-4.4 (2.33)	-2.2 (2.28)
CFB at 120 minutes, Adjusted Mean (SE)	-11.0 (3.00)	-5.3 (3.00)	-8.0 (2.37)	-4.6 (2.34)
Treatment Comparisons				
60 minutes	**Adjusted Mean Difference**[1]		**95% CI**	**P Value**[2]
A vs B	-4.5		-12.5, 3.5	0.2669
C vs D	-2.2		-8.3, 4.0	
A vs C	1.4		-5.8, 8.5	
120 minutes	**Adjusted Mean Difference**[1]		**95% CI**	**P Value**[2]
A vs B	-5.7		-13.9, 2.5	0.1706
C vs D	-3.4		-9.7, 2.9	
A vs C	-3.0		-10.3, 4.3	
[1] A negative difference favours the first named treatment; [2] A hierarchical testing procedure is used such that p-values are only presented if the preceding treatment comparison is statistically significant (p<0.05).				
9. Number of inaccurate and missed responses to DAT Cognitive test				
Inaccurate Responses	**A**	**B**	**C**	**D**
Baseline, Mean (SE)	21.5 (1.07)	22.6 (1.65)	23.0 (1.22)	21.2 (0.94)
CFB at 60 minutes, Mean (SE)	-6.5 (1.02)	-4.2 (1.11)	-5.4 (0.87)	-3.3 (0.81)
CFB at 120 minutes, Mean (SE)	-7.1 (1.01)	-4.9 (1.10)	-5.6 (0.86)	-5.0 (0.98)
Missed Responses	**A**	**B**	**C**	**D**
Baseline, Mean (SE)	23.1 (1.89)	23.2 (2.29)	24.7 (1.48)	23.5 (1.62)
CFB at 60 minutes, Mean (SE)	-10.2 (1.27)	-7.6 (2.08)	-9.8 (1.19)	-6.2 (1.50)
CFB at 120 minutes, Mean (SE)	-12.2 (1.54)	-9.1 (2.27)	-10.2 (1.43)	-7.8 (1.58)

Safety Results: An on therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. An on therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication.
AE – On-Therapy: No AEs were reported during the study period.
SAE - On-Therapy: No SAEs were reported during the study period.