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 No.:** C6930943

**Title:** Effects of a Common Cold Treatment on Cognitive Function

**Rationale:** A reduction in alertness and lower levels of performance are commonly associated with the common cold. Paracetamol has been shown to be more effective than placebo in treating symptoms associated with upper respiratory tract infection; caffeine has been shown to increase levels of alertness and improve performance of people suffering from colds. This study will investigate any improvement in alertness and performance based on cognitive function and mood assessment in subjects suffering the common cold, when taking a novel paracetamol and caffeine combination versus paracetamol alone.

**Phase:** 4

**Study Period:** 3rd February 2011 to 11th April 2011

**Study Design:** Single centre, 2 period, 2 treatment crossover, single blind (investigator blind) study

**Centre:** 1, UK

**Indication:** Common Cold

**Treatment:**

*Study Treatment*

2 x paracetamol and caffeine 500 milligram (mg)/65 mg soluble tablets (The tablets were dissolved in 200 millilitre (mL) water)

*Reference Therapy*

1 x paracetamol 1000 mg soluble powder sachet (The powder was dissolved in 200 mL water with 1.5 mL Robinsons No Added sugar orange concentrate)

**Objectives:**

*Primary Objective:*

To assess the change in alertness level in people suffering from the common cold, 30 minutes following a dose of soluble paracetamol and caffeine compared to soluble paracetamol. This was assessed from the number of valid responses to the rapid visual information processing (RVIP).

*Secondary Objectives*:

1. To assess the change in alertness level in people suffering from the common cold, following a dose of soluble paracetamol and caffeine compared to soluble paracetamol. This was assessed from the number of valid responses to the RVIP at the 60-minute time point, and the mean valid reaction time at the 30-minute and 60-minute time points.
2. To assess the change in mood in people suffering from the common cold, following a dose of soluble paracetamol and caffeine compared to soluble paracetamol.
3. To assess the change in alertness level in people suffering from the common cold, following a dose of soluble paracetamol and caffeine compared to soluble paracetamol, using a sustained and divided attention task. This was assessed from the number of valid responses to the task, and the mean valid reaction time at the 30-minute and 60-minute time points.

**Primary Efficacy Variable:**

Change from baseline in the number of valid responses (from the RVIP) at 30 minutes.

**Secondary Efficacy Variables:**

1. From the RVIP, change from baseline in:
    - The number of valid responses at 60 minutes
    - The mean valid reaction time at 30 and 60 minutes

- The number of incorrect responses at 30 and 60 minutes
- The number of missed responses at 30 and 60 minutes

2. From the sustained auditory and divided attention tasks, change from baseline in:
   - The number of valid responses at 30 and 60 minutes
   - The mean valid reaction time at 30 and 60 minutes
   - The number of incorrect responses at 30 and 60 minutes
   - The number of missed responses at 30 and 60 minutes
3. Change from baseline in the assessment of mood from the Mood, Alertness and Physical Sensations Scales (MAPSS).

**Statistical Methods:**

For the number of valid responses and mean valid reaction time from each of the cognitive function tests, and the mood evaluation questionnaire, the planned analysis specified in the protocol and statistical analysis plan was to perform a random effects analysis of covariance (ANCOVA) on the change from baseline to 30 and 60 minutes.

The ANCOVA model was to include subject (as a random effect), treatment group and study period as factors and two baseline terms as covariates; (i) the subject-level baseline value calculated as the mean baseline across both periods within a subject, and (ii) the period level baseline minus the subject-level baseline. The number of incorrect responses and number of missed responses to each of the cognitive function tests were summarised by treatment group using descriptive statistics, including mean, median, standard deviation (SD), minimum and maximum. After unblinding the study, the data was reviewed to check the model assumptions. At this stage the statistician was unblinded but the other report authors remained blinded as this was prior to the validation of statistical analysis and discussion of results with the medical team. During this unblinded review, it was noted that for the number of valid responses parameter, in subjects randomised to the paracetamol +caffeine followed by paracetamol treatment sequence, the period 2 baseline scores were notably higher compared to the period 1 baseline scores. This suggested there may have been some residual effects from the paracetamol + caffeine treatment taken in the first period carrying over to the baseline phase of the second period. Since the period 2 baseline scores were evidently not independent of the treatment taken in period 1, the planned analysis of covariance with period-level or subject-level baseline scores as covariates was deemed inappropriate as the model assumptions did not hold. Inspection of the raw treatment group means in each of the 2 study periods suggested that although the period 2 baseline was being impacted by the previous treatment, the response endpoint at 30 and 60 minutes post-treatment was not impacted. Therefore, two further alternative models described in the SAP Addendum were proposed.

The principal analysis would be an analysis of variance (ANOVA), ignoring the baseline scores. This is a more statistically robust approach when there is some doubt over whether the washout period is sufficiently long. In addition, a sensitivity analysis using only data from period 1 (with the period 1 baseline score as a covariate) was performed to assess the robustness of the principal analysis described above. All results are presented in the end of text tables, but conclusions have been drawn from the ANOVA without adjustment for baseline scores.

**Study Population:**

| | **Overall** |
|---|---|
| Number of Subjects: | |
| Screened, N | 75 |
| Randomised, N | 72 |
| Completed, n (%) | 71(98.6) |
| Total Number Subjects Withdrawn, n (%) | 1(1.4) |
| Withdrawal of Consent, n (%) | 1(1.4) |
| **Demographics (Intent To Treat [ITT] Population N= 71)** | **Overall** |
| Female n (%): Male n (%) | 47 (66.2):24 (33.8) |
| Mean Age, years (SD) | 20.8 (4.19) |
| **Race, n (%)** | |
| Asian | 3 (4.2) |
| White | 68 (95.8) |

**Primary Efficacy Results:** The primary parameter for assessment of efficacy was the change from baseline in the number of valid responses (from the RVIP) at 30 minutes post−dose. The assessment at 60 minutes post-dose was a secondary efficacy parameter, but for presentation purposes both time-points are presented here.

**Table 1: Analysis of Number of Valid Responses to the RVIP (Change from Baseline) - Principal Analysis**

| Time point | Mean(SE)[1] | | Difference (Adj. Mean)[2] | 95% CI (lower, upper) | p-value |
|---|---|---|---|---|---|
| | 1000mg paracetamol+130mg caffeine(N=71) | 1000mg paracetamol (N=71) | | | |
| **Baseline** | 25.8(1.19) | 28.9(1.11) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | 4.8(0.80) | 1.3(0.80) | 3.6 | (1.5,5.6) | 0.0008 |
| **60 minutes** | 7.1(0.93) | 0.6(0.93) | 6.5 | (4.5,8.4) | <0.0001 |

*1 Raw absolute means are presented at baseline. Adjusted mean changes from baseline are presented at 30 and 60 minutes.*
*2 A positive difference favours the paracetamol + caffeine treatment.*

**Table 2: Sensitivity Analysis of Number of Valid Responses to the RVIP using Period 1 Only (Change from Baseline)-ITT Population**

| Time point | Mean(SE)[1] | | Difference (Adj. Mean)[2] | 95% CI (lower, upper) | p-value |
|---|---|---|---|---|---|
| | 1000mg paracetamol+130mg caffeine(N=36) | 1000mg paracetamol (N=35) | | | |
| **Baseline** | 23.8(1.48) | 26.6(1.49) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | 4.8(1.09) | 1.8(1.09) | 3.1 | (-0.1,6.2) | 0.0535 |
| **60 minutes** | 9.0(1.27) | 2.2(1.28) | 6.8 | (3.2,10.4) | 0.0004 |

*1 Raw absolute means are presented at baseline. Adjusted mean changes from baseline are presented at 30 and 60 minutes.*
*2 A positive difference favours the paracetamol + caffeine treatment.*

**Secondary Efficacy Results: RVIP**

**Table 3: Analysis of Mean Valid Reaction Time (msec) to the RVIP (Change from Baseline)-ITT Population-*Principal***

| Time point | Mean(SE)[1] | | Difference (Adj. Mean)[2] | 95% CI (lower, upper) | p-value |
|---|---|---|---|---|---|
| | 1000mg paracetamol+130mg caffeine(N=71) | 1000mg paracetamol (N=71) | | | |
| **Baseline** | 405.25(7.030) | 406.64(6.686) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | 6.00(3.916) | 1.88(3.916) | 4.12 | (-6.18,14.41) | 0.4279 |
| **60 minutes** | 0.08(3.983) | -4.85(3.954) | 4.92 | (-6.18,16.02) | 0.3820 |

**Table 4: Sensitivity Analysis of Mean Valid Reaction Time (msec) to the RVIP using Period 1 Only (Change from Baseline) - ITT Population**

| Time point | Mean(SE)1 | | Difference (Adj. Mean)2 | 95% CI (lower, upper) | P-value |
|---|---|---|---|---|---|
| | 1000mg paracetamol+130mg caffeine(N=36) | 1000mg paracetamol (N=35) | | | |
| **Baseline** | 402.82(11.204) | 409.03(9.174) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | 9.39(5.757) | 1.72(5.757) | 7.66 | (-8.60,23.93) | 0.3504 |
| **60 minutes** | 3.13(5.840) | -0.83(5.923) | 3.96 | (-12.65,20.57) | 0.6360 |

*1 Raw absolute means are presented at baseline. Adjusted mean changes from baseline are presented at 30 and 60 minutes.*
*2 A negative difference favours the paracetamol + caffeine treatment.*

**Table 5: Number of Incorrect and Missed Responses to the RVIP (Change from Baseline)**

| Parameter | Time point | Mean (SE) | |
|---|---|---|---|
| | | 1000mg paracetamol+130mg caffeine (N=71) | 1000mg paracetamol (N=71) |
| **No of Incorrect Responses** | Baseline | 36.1(3.14) | 36.4 (4.02) |
| | Change from Baseline to 30 | -2.3(1.57) | -2.7 (1.52) |
| | Change from Baseline to 60 | -1.7(1.93) | -2.7 (1.80) |
| **No of Missed Responses** | Baseline | 46.2 (1.19) | 43.1 (1.11) |
| | Change from Baseline to 30 | -4.8 (0.69) | -1.3 (0.89) |
| | Change from Baseline to 60 | -7.1 (0.90) | -0.6 (1.00) |

**Secondary Efficacy Results: Sustained and Divided Attention**

**Table 6: Sustained Auditory Task: Analysis of Number of Valid Responses to the Sustained Auditory Task (Change from Baseline) - ITT Population**

| Time point | Mean (SE) [1] | | Difference (Adj. Mean) [2] | 95% CI (lower, upper) | p-value |
|---|---|---|---|---|---|
| | 1000mg paracetamol+130mg caffeine (N=71) | 1000mg paracetamol (N=71) | | | |
| **Baseline** | 44.0 (0.73) | 45.4 (0.62) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | 1.8 (0.52) | -0.5 (0.51) | 2.3 | (0.8, 3.7) | 0.0023 |
| **60 minutes** | 1.5 (0.55) | -0.7 (0.55) | 2.2 | (0.7, 3.8) | 0.0045 |

*1 Raw absolute means are presented at baseline. Adjusted mean changes from baseline are presented at 30 and 60 minutes.*
*2 A positive difference favours the first named treatment.*

**Table 7: Sustained Auditory Task: Sensitivity Analysis of Number of Valid Responses to the Sustained Auditory Task using Period 1 Only (Change from Baseline) - ITT Population**

| Time point | Mean (SE) [1] | | Difference (Adj. Mean) [2] | 95% CI (lower, upper) | p-value |
|---|---|---|---|---|---|
| | 1000mg paracetamol+130mg caffeine(N=36) | 1000mg paracetamol (N=35) | | | |
| **Baseline** | 43.7 (1.01) | 45.0 (0.69) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | 2.1 (0.64) | -0.9 (0.63) | 3.0 | (1.2, 4.8) | 0.0015 |
| **60 minutes** | 1.9 (0.81) | -1.4 (0.81) | 3.3 | (1.1, 5.6) | 0.0049 |

*1 Raw absolute means are presented at baseline. Adjusted mean changes from baseline are presented at 30 and 60 minutes.*
*2 A positive difference favours the paracetamol + caffeine treatment.*

**Table 8: Analysis of Mean Valid Reaction Time (msec) to the Sustained Auditory Task (Change from Baseline) - Principal Analysis**

| Time point | Mean (SE) [1] | | Difference (Adj. Mean) [2] | 95% CI (lower, upper) | p-value |
|---|---|---|---|---|---|
| | 1000mg paracetamol+130mg caffeine (N=71) | 1000mg paracetamol (N=71) | | | |
| **Baseline** | 371.02 (3.537) | 367.95 (3.690) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | -6.49 (2.797) | -6.18 (2.755) | -0.31 | (-8.09, 7.47) | 0.9368 |
| **60 minutes** | -10.69 (3.120) | -9.45 (3.097) | -1.24 | (-9.92, 7.44) | 0.7764 |

*1 Raw absolute means are presented at baseline. Adjusted mean changes from baseline are presented at 30 and 60 minutes.*
*2 A negative difference favours the paracetamol + caffeine treatment.*

**Table 9: Sensitivity Analysis of Mean Valid Reaction Time (msec) to the Sustained Auditory Task using Period 1 only (Change from Baseline) - ITT Population**

| Time point | Mean (SE)[1] | | Difference (Adj. Mean) [2] | 95% CI (lower, upper) | p-value |
|---|---|---|---|---|---|
| | 1000mg paracetamol+130mg caffeine(N=36) | 1000mg paracetamol (N=35) | | | |
| **Baseline** | 368.87(4.633) | 383.36(4.001) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | -5.98(3.267) | -8.92(3.218) | 2.95 | (-6.39,12.28) | 0.5308 |
| **60 minutes** | -12.23(3.941) | -12.36(3.941) | 0.13 | (-11.21,11.47) | 0.9819 |

*1 Raw absolute means are presented at baseline. Adjusted mean changes from baseline are presented at 30 and 60 minutes.*
*2 A negative difference favours the paracetamol + caffeine treatment.*

**Table 10: Number of Incorrect and Missed Responses to the Sustained Auditory Task (Change from Baseline) -ITT Population**

| Parameter | Time point | Mean (SE) | |
|---|---|---|---|
| | | 1000 mg paracetamol + 130 mg caffeine (N=71) | 1000 mg paracetamol (N=71) |
| **No. Incorrect Responses** | **Baseline** | 13.9 (0.86) | 11.7 (0.86) |
| | **Change from baseline to 30 mins** | -2.3 (0.63) | 0.1 (0.65) |
| | **Change from baseline to 60 mins** | -3.6 (0.71) | 0.6 (0.72) |
| **No. Missed Responses** | **Baseline** | 6.0 (0.73) | 4.6 (0.62) |
| | **Change from baseline to 30 mins** | -1.8 (0.59) | 0.5 (0.44) |
| | **Change from baseline to 60 mins** | -1.5 (0.54) | 0.7 (0.55) |

**Divided Attention Task**

**Table 11: Analysis of Number of Valid Responses to the Divided Attention Task (Change from Baseline) - ITT Population**

| Time point | Mean (SE) [1] | | Difference [2] (Adj. Mean) | 95% CI (Lower, Upper) | p-value |
|---|---|---|---|---|---|
| | 1000 mg paracetamol + 130 mg caffeine (N=71) | 1000 mg paracetamol (N=71) | | | |
| **Baseline** | 81.7 (1.40) | 85.4 (1.10) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | 6.8 (1.00) | 2.0 (0.99) | 4.8 | (2.0, 7.6) | 0.0009 |
| **60 minutes** | 7.4 (1.01) | 1.9 (1.00) | 5.5 | (2.7, 8.3) | 0.0002 |

*1 Raw absolute means are presented at baseline. Adjusted mean changes from baseline are presented at 30 and 60 minutes.*
*2 A positive difference favours the paracetamol + caffeine treatment*

**Table 12: Sensitivity Analysis of Number of Valid Responses to the Divided Attention Task using Period 1 Only (Change from Baseline) - ITT Population**

| Time point | Mean (SE)[1] | | Difference[2] (Adj. Mean) | 95% CI (Lower, Upper) | p-value |
|---|---|---|---|---|---|
| | 1000 mg paracetamol + 130 mg caffeine | 1000 mg paracetamol (N=35) | | | |
| **Baseline** | 79.9 (2.05) | 82.6 (1.52) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | 8.9 (1.08) | 4.0 (1.06) | 4.9 | (1.9, 8.0) | 0.0018 |
| **60 minutes** | 9.4 (1.24) | 3.5 (1.24) | 5.9 | (2.4, 9.4) | 0.0014 |

*1 Raw absolute means are presented at baseline. Adjusted mean changes from baseline are presented at 30 and 60 minutes.*
*2 A positive difference favours the paracetamol + caffeine treatment.*

**Table 13 - Analysis of Mean Valid Reaction Time (msec) to the Divided Attention Task (Change from Baseline) - ITT Population**

| Time point | Mean (SE)[1] | | Difference[2] (Adj. Mean) | 95% CI (Lower, Upper) | p-value |
|---|---|---|---|---|---|
| | 1000 mg paracetamol + 130 mg caffeine | 1000 mg paracetamol (N=71) | | | |
| **Baseline** | 361.53 (2.721) | 365.68 (2.381) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | 1.65 (2.104) | -7.42 (2.074) | 9.08 | (3.24, 14.92) | 0.0026 |
| **60 minutes** | -5.49 (2.444) | -12.39 (2.426) | 6.90 | (0.18, 13.61) | 0.0442 |

*1 Raw absolute means are presented at baseline. Adjusted mean changes from baseline are presented at 30 and 60 minutes.*
*2 A negative difference favours the paracetamol + caffeine treatment*

**Table 14: Sensitivity Analysis of Mean Valid Reaction Time (msec) to the Divided Attention Task using Period 1 Only (Change from Baseline) - ITT Population**

| Time point | Mean (SE)[1] | | Difference[2] (Adj. Mean) | 95% CI (Lower, Upper) | p-value |
|---|---|---|---|---|---|
| | 1000 mg paracetamol + 130 mg caffeine | 1000 mg paracetamol (N=35) | | | |
| **Baseline** | 359.26 (3.200) | 368.85 (3.090) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | 4.19 (2.733) | -0.17 (2.693) | 4.37 | (-3.41, 12.14) | 0.2661 |
| **60 minutes** | -4.66 (3.051) | -8.06 (3.051) | 3.40 | (-5.35, 12.16) | 0.4403 |

*1 Raw absolute means are presented at baseline. Adjusted mean changes from baseline are presented at 30 and 60 minutes.*
*2 A negative difference favours the paracetamol + caffeine treatment.*

**Table 15: Number of Incorrect and Missed Responses to the Divided Attention Task (Change from Baseline) - ITT Population**

| Parameter | Time point | Mean (SE) | |
|---|---|---|---|
| | | 1000 mg paracetamol + 130 mg caffeine (N=71) | 1000 mg paracetamol (N=71) |
| **No. Incorrect Responses** | **Baseline** | 21.6 (1.13) | 19.3 (1.07) |
| | **Change from baseline to 30 mins** | -5.4 (0.83) | -1.4 (0.83) |
| | **Change from baseline to 60 mins** | -5.2 (0.77) | -0.2 (0.92) |
| **No. Missed** | **Baseline** | 18.3 (1.40) | 14.6 (1.10) |

| | | | |
|---|---|---|---|
| | **Change from baseline to 30 mins** | -6.7 (1.19) | -2.0 (0.83) |
| **Responses** | **Change from baseline to 60 mins** | -7.4 (1.24) | -1.9 (0.75) |

**Table 16: Analysis of the MAPSS Questionnaire (Change from Baseline) - ITT Population**

| **Time point** | **Mean (SE)[1]** | | **Difference[2] (Adj. Mean)** | **95% CI (Lower, Upper)** | **p-value** |
|---|---|---|---|---|---|
| | 1000 mg paracetamol + 130 mg caffeine (N=71) | 1000 mg paracetamol (N=71) | | | |
| **'ALERTNESS'** | | | | | |
| **Baseline** | 3.8 (0.14) | 4.0 (0.16) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | 0.8 (0.12) | 0.2 (0.12) | 0.6 | (0.2, 0.9) | 0.0008 |
| **60 minutes** | 0.7 (0.13) | 0.1 (0.13) | 0.6 | (0.2, 0.9) | 0.0019 |
| **'ANXIETY'** | | | | | |
| **Baseline** | 7.3 (0.12) | 7.2 (0.12) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | 0.2 (0.08) | 0.2 (0.08) | -0.1 | (-0.3, 0.2) | 0.5786 |
| **60 minutes** | 0.3 (0.08) | 0.4 (0.08) | -0.1 | (-0.3, 0.1) | 0.3987 |
| **'HEADACHE'** | | | | | |
| **Baseline** | 6.4 (0.16) | 6.4 (0.18) | | | |
| **Change from baseline** | | | | | |
| **30 minutes** | 0.4 (0.10) | 0.4 (0.10) | 0.0 | (-0.3, 0.3) | 0.8342 |
| **60 minutes** | 0.6 (0.10) | 0.6 (0.10) | 0.0 | (-0.3, 0.3) | 0.7992 |

*Questions answered on a 9-point scale.*
*1 Raw absolute means are presented at baseline. Adjusted mean changes from baseline are presented at 30 and 60 minutes.*
*2 A positive difference favours the paracetamol+caffeine treatment.*

**Safety Results:** No adverse events were reported

**Serious Adverse Events - On-Therapy**: No SAE occurred on either treatment.