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GSK Medicine: Paracetamol and Caffeine
Study Number: A2370327
Title: A Placebo Controlled Clinical Study to Investigate the Efficacy of a Combination Analgesic Treatment Compared to its Individual Components in Primary Dysmenorrhoea
Rationale: To investigate the effect of paracetamol and caffeine compared to paracetamol alone, to caffeine alone and to placebo in the treatment of dysmenorrhoea symptoms.
Phase: III
Study Period: 13 Jan 2005 to 23 Jun 2005
Study Design: This was a single centre, double blind, randomised, three way crossover, incomplete block design, placebo controlled, outpatient study in females. All subjects received paracetamol + caffeine and paracetamol alone, with half of subjects receiving caffeine alone and other half of subjects receiving placebo. Subjects self medicated as soon as they experienced sufficient pain associated with menstruation. Subjects recorded period pain/relief, cramping, backache and tiredness assessments prior to, and at various time points up to 6 hours post dosing using Verbal Rating Scales (VRS) in a diary card. Period pain relief was rated on a 5 point VRS (0 = no relief, 4 = complete relief); period pain, cramping, backache and tiredness were rated on a 4 point VRS (0 = none, 3 = severe).
Centre: 1 centre in United Kingdom
Indication: Pain
Treatments: Test Product: Paracetamol Extra tablets: administered as 2 x Paracetamol Extra tablets (1000mg paracetamol + 130mg caffeine) orally with at least half a glass of water. Reference Products: <ol style="list-style-type: none"> 1. Paracetamol tablets: administered as 2 x Paracetamol tablets (1000mg paracetamol) orally with at least half a glass of water. 1. Caffeine tablets: administered as 2 x Caffeine tablets (130mg caffeine) orally with at least half a glass of water. 2. Placebo tablets: administered as 2 x Placebo tablets orally with at least half a glass of water.
Objective: Primary objectives: <ol style="list-style-type: none"> 1. To compare the efficacy of a single dose of paracetamol and caffeine with a single dose of paracetamol alone for pain relief in subjects with primary dysmenorrhoea symptoms. 2. To compare the efficacy of a single dose of paracetamol and caffeine with a single dose of caffeine alone for pain relief in subjects with primary dysmenorrhoea symptoms. Secondary Objectives: <ol style="list-style-type: none"> 1. To compare the efficacy of a single dose of paracetamol and caffeine with a single dose of paracetamol alone, caffeine alone and placebo for abdominal cramping, backache and tiredness in subjects with primary dysmenorrhoea symptoms. 2. To compare the efficacy of a single dose of paracetamol and caffeine with a single dose of placebo for pain relief in subjects with primary dysmenorrhoea symptoms. 3. To compare the efficacy of a single dose of paracetamol alone with a single dose of placebo for pain relief, abdominal cramping, backache and tiredness in subjects with primary dysmenorrhoea symptoms. 4. To compare safety as assessed by adverse events (AEs).
Primary Outcome Endpoint: Total Pain Relief (TOTPAR): TOTPAR _{0-2 hours} for pain relief
Secondary Outcome Endpoints: <ol style="list-style-type: none"> 1. Pain relief at 0.5, 1 and 2 hours 2. TOTPAR_{0-3 hours}, TOTPAR_{0-4 hours} and TOTPAR_{0-6 hours} for pain relief 3. Abdominal cramping intensity difference from baseline at 0.5, 1 and 2 hours. 4. Sum of Abdominal Cramp Intensity Difference Score (SACID): SACID_{0-2 hours}, SACID_{0-3 hours}, SACID_{0-4 hours}

and SACID _{0-6 hours} for abdominal cramping.				
5. Backache intensity difference from baseline at 0.5, 1 and 2 hours.				
6. Sum of Backache Intensity Difference Score (SBID): SBID _{0-2 hours} , SBID _{0-3 hours} , SBID _{0-4 hours} and SBID _{0-6 hours} for backache.				
7. Tiredness intensity difference from baseline at 0.5, 1 and 2 hours.				
8. Sum of Tiredness Intensity Difference Score (STID): STID _{0-2 hours} , STID _{0-3 hours} , STID _{0-4 hours} and STID _{0-6 hours} for tiredness.				
9. Proportion of subjects using rescue medication.				
Statistical Methods:				
The efficacy variables were analysed by an analysis of covariance (ANCOVA) model appropriate for a crossover design. The model included subject, period, treatment and the appropriate pre-dose assessment as a covariate. Differences between proportions of subjects taking rescue medication were analysed using McNemar's test. All statistical testing was performed at the 5% significance level and p-values and 95% confidence intervals (CIs) are presented for the following treatment comparisons:				
<ul style="list-style-type: none">• Paracetamol and caffeine versus (vs.) paracetamol alone• Paracetamol and caffeine vs. caffeine alone• Paracetamol and caffeine vs. placebo• Paracetamol vs. placebo• No adjustment was made for multiple testing.				
Study Population:				
Subject Disposition				
	Overall			
Subjects Randomized, n	320			
Number of subjects in safety population, n	320			
Number of subjects in intent to treat (ITT) population, n	310			
Number of subjects not in ITT population, n	10			
Reason for not in ITT population ^[1] , n				
Lost to Follow-Up	2			
Protocol Deviation	1			
Withdrawal of Consent	1			
Other	6			
Number of ITT Subjects Not Completing Study, n	21			
Protocol Deviation	5			
Other	16			
<i>[1] Did not dose or complete a post-baseline efficacy assessment.</i>				
Demographics (All Randomized Subjects)				
	Overall			
N	320			
Sex, n (%)				
Females	320 (100.0)			
Mean Age, years (SD)	21.27 (2.834)			
Race, n (%)				
Caucasian	297 (92.8)			
Black	3 (0.9)			
Asian	20 (6.3)			
Primary Outcome Results (ITT population, N=310):				
Table 1: TOTPAR_{0-2hour}				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	298	301	151	151
Mean (SD)	2.90 (1.945)	2.62 (1.792)	2.38 (1.802)	2.32 (1.874)
Adjusted Mean ^[1]	2.89	2.62	2.38	2.32
Treatment comparison				
Paracetamol + Caffeine vs. Paracetamol				

Mean Difference ^[2]	0.27			
95% CI	(0.03,0.52)			
p-value	0.0302			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.52			
95% CI	(0.20,0.83)			
p-value	0.0012			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.57			
95% CI	(0.26,0.88)			
p-value	0.0003			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.30			
95% CI	(-0.01,0.61)			
p-value	0.0588			
[1] Least squares mean from ANCOVA adjusted for subject, period, treatment and baseline covariate.				
[2] Mean difference is the difference in adjusted means.				
Secondary Outcome Results (ITT population, N=310):				
Table 2: Pain relief at 0.5, 1 and 2 hours				
At 0.5 hour				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	298	301	151	151
Mean (SD)	0.68 (0.911)	0.53 (0.789)	0.52 (0.901)	0.56 (0.845)
Adjusted Mean ^[1]	0.68	0.54	0.51	0.56
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.14			
95% CI	(0.03,0.26)			
p-value	0.0148			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.17			
95% CI	(0.02,0.31)			
p-value	0.0252			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.13			
95% CI	(-0.02,0.27)			
p-value	0.0906			
Paracetamol vs. Placebo				
Mean Difference ^[2]	-0.02			
95% CI	(-0.16,0.13)			
p-value	0.8108			
At 1 hour				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	298	301	151	151
Mean (SD)	1.38 (1.104)	1.21 (1.056)	1.15 (1.012)	1.11(1.068)
Adjusted Mean ^[1]	1.37	1.21	1.15	1.11
Treatment comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.16			
95% CI	(0.02,0.31)			
p-value	0.0288			
Paracetamol + Caffeine vs. Caffeine				

Mean Difference ^[2]	0.22			
95% CI	(0.04,0.41)			
p-value	0.0187			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.26			
95% CI	(0.08,0.44)			
p-value	0.0056			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.10			
95% CI	(-0.09,0.28)			
p-value	0.2987			
At 2 hour				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	298	301	151	151
Mean (SD)	1.87 (1.199)	1.74 (1.145)	1.54 (1.118)	1.48 (1.177)
Adjusted Mean ^[1]	1.87	1.75	1.54	1.49
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.12			
95% CI	(-0.04,0.28)			
p-value	0.1451			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.32			
95% CI	(0.12,0.53)			
p-value	0.0016			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.38			
95% CI	(0.18,0.58)			
p-value	0.0002			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.26			
95% CI	(0.06,0.46)			
p-value	0.0114			
[1] Least squares mean from ANCOVA adjusted for subject, period, treatment and baseline covariate.				
[2] Mean difference is the difference in adjusted means.				
Table 3: TOTPAR ₀₋₃ hours, TOTPAR ₀₋₄ hours and TOTPAR ₀₋₆ hours for pain relief				
TOTPAR ₀₋₃ hours				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	298	301	151	151
Mean (SD)	5.07 (2.952)	4.62 (2.796)	4.12 (2.755)	4.03 (2.909)
Adjusted Mean ^[1]	5.06	4.64	4.08	4.07
Treatment comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.42			
95% CI	(0.05,0.79)			
p-value	0.0266			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.97			
95% CI	(0.50,1.45)			
p-value	< 0.0001			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.99			
95% CI	(0.52,1.46)			

p-value	< 0.0001			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.57			
95% CI	(0.10,1.04)			
p-value	0.0174			
TOTPAR _{0-4 hours}				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	298	301	151	151
Mean (SD)	7.34 (4.033)	6.78 (3.860)	5.93 (3.888)	5.76 (4.073)
Adjusted Mean ^[1]	7.34	6.80	5.89	5.82
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.53			
95% CI	(0.03,1.04)			
p-value	0.0389			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	1.45			
95% CI	(0.80,2.09)			
p-value	< 0.0001			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	1.52			
95% CI	(0.88,2.16)			
p-value	< 0.0001			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.99			
95% CI	(0.34,1.63)			
p-value	0.0026			
TOTPAR _{0-6 hours}				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	298	301	151	151
Mean (SD)	11.70 (6.281)	10.89 (6.221)	9.51 (6.293)	9.31 (6.642)
Adjusted Mean ^[1]	11.72	10.93	9.49	9.38
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.79			
95% CI	(0.00,1.57)			
p-value	0.0500			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	2.23			
95% CI	(1.22,3.24)			
p-value	< 0.0001			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	2.34			
95% CI	(1.34,3.34)			
p-value	< 0.0001			
Paracetamol vs. Placebo				
Mean Difference ^[2]	1.55			
95% CI	(0.55,2.56)			
p-value	0.0024			
^[1] Least squares mean from ANCOVA adjusted for subject, period, treatment and baseline covariate.				
^[2] Mean difference is the difference in adjusted means.				
Table 4: Summary and Analysis of Abdominal Cramping Intensity Difference From Baseline at 0.5, 1 and 2 Hours				

At 0.5 hours				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	297	301	150	151
Mean (SD)	0.25 (0.544)	0.14 (0.510)	0.17 (0.511)	0.18 (0.530)
Adjusted Mean ^[1]	0.25	0.14	0.17	0.17
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.11			
95% CI	(0.04,0.19)			
p-value	0.0031			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.08			
95% CI	(-0.01,0.18)			
p-value	0.0882			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.09			
95% CI	(-0.01,0.18)			
p-value	0.0757			
Paracetamol vs. Placebo				
Mean Difference ^[2]	-0.03			
95% CI	(-0.12,0.07)			
p-value	0.5502			
At 1 hour				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	297	301	150	151
Mean (SD)	0.65 (0.746)	0.56 (0.749)	0.54 (0.692)	0.50 (0.729)
Adjusted Mean ^[1]	0.66	0.56	0.54	0.49
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.11			
95% CI	(0.01,0.20)			
p-value	0.0367			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.12			
95% CI	(-0.01,0.24)			
p-value	0.0619			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.17			
95% CI	(0.05,0.29)			
p-value	0.0077			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.06			
95% CI	(-0.06,0.19)			
p-value	0.3109			
At 2 hour				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	297	301	150	151
Mean (SD)	0.95 (0.802)	0.87 (0.812)	0.78 (0.785)	0.75 (0.791)
Adjusted Mean ^[1]	0.96	0.87	0.78	0.75
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.09			

95% CI	(-0.02,0.20)			
p-value	0.1111			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.18			
95% CI	(0.04,0.32)			
p-value	0.0129			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.21			
95% CI	(0.07,0.35)			
p-value	0.0027			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.12			
95% CI	(-0.02,0.26)			
p-value	0.0830			
[1] Least squares mean from ANCOVA adjusted for subject, period, treatment and baseline covariate.				
[2] Mean difference is the difference in adjusted means.				
Table 5: Summary and Analysis of Summed Abdominal Cramping Intensity Difference - SACID ₀₋₂ , 0-3, 0-4 and 0-6				
Hours				
SACID ₀₋₂ hours				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	297	301	150	151
Mean (SD)	1.40 (1.259)	1.21 (1.244)	1.13 (1.201)	1.10 (1.211)
Adjusted Mean ^[1]	1.42	1.22	1.14	1.07
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.20			
95% CI	(0.03,0.36)			
p-value	0.0182			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.28			
95% CI	(0.07,0.48)			
p-value	0.0099			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.34			
95% CI	(0.13,0.55)			
p-value	0.0013			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.14			
95% CI	(-0.07,0.35)			
p-value	0.1807			
SACID ₀₋₃ hours				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	297	301	150	151
Mean (SD)	2.52 (1.957)	2.20 (1.943)	2.04 (1.874)	2.00 (1.914)
Adjusted Mean ^[1]	2.54	2.20	2.04	1.97
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.34			
95% CI	(0.08,0.59)			
p-value	0.0091			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.50			
95% CI	(0.18,0.82)			
p-value	0.0023			

Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.57			
95% CI	(0.25,0.89)			
p-value	0.0005			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.23			
95% CI	(-0.08,0.55)			
p-value	0.1484			
SACID ₀₋₄ hours				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	297	301	150	151
Mean (SD)	3.68 (2.652)	3.30 (2.611)	2.99 (2.580)	2.92 (2.711)
Adjusted Mean ^[1]	3.72	3.32	3.00	2.87
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.40			
95% CI	(0.07,0.74)			
p-value	0.0171			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.72			
95% CI	(0.30,1.14)			
p-value	0.0009			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.85			
95% CI	(0.43,1.27)			
p-value	< 0.0001			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.45			
95% CI	(0.03,0.87)			
p-value	0.0364			
SACID ₀₋₆ hours				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	297	301	150	151
Mean (SD)	5.99 (4.118)	5.50 (4.025)	4.87 (4.117)	4.82 (4.379)
Adjusted Mean ^[1]	6.07	5.53	4.88	4.73
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.54			
95% CI	(0.05,1.04)			
p-value	0.0302			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	1.19			
95% CI	(0.56,1.82)			
p-value	0.0002			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	1.34			
95% CI	(0.72,1.97)			
p-value	< 0.0001			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.80			
95% CI	(0.17,1.42)			
p-value	0.0126			

[1] Least squares mean from ANCOVA adjusted for subject, period, treatment and baseline covariate.				
[2] Mean difference is the difference in adjusted means.				
Table 6: Summary and Analysis of Backache Intensity Difference From Baseline at 0.5, 1 and 2 Hours				
At 0.5 hours				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	176	176	89	87
Mean (SD)	0.21(0.508)	0.13 (0.449)	0.06 (0.436)	0.09 (0.448)
Adjusted Mean ^[1]	0.20	0.12	0.08	0.09
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.08			
95% CI	(-0.01,0.17)			
p-value	0.0657			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.13			
95% CI	(0.02,0.24)			
p-value	0.0223			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.12			
95% CI	(0.01,0.23)			
p-value	0.0370			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.03			
95% CI	(-0.07,0.14)			
p-value	0.5317			
At 1 hour				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	176	176	89	87
Mean (SD)	0.40 (0.615)	0.32 (0.624)	0.29 (0.505)	0.29 (0.714)
Adjusted Mean ^[1]	0.39	0.31	0.33	0.27
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.08			
95% CI	(-0.04,0.19)			
p-value	0.1809			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.05			
95% CI	(-0.09,0.19)			
p-value	0.4421			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.12			
95% CI	(-0.03,0.26)			
p-value	0.1082			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.04			
95% CI	(-0.10,0.18)			
p-value	0.5878			
At 2 hour				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	176	176	89	87
Mean (SD)	0.64 (0.704)	0.57 (0.832)	0.40 (0.686)	0.49 (0.834)
Adjusted Mean ^[1]	0.63	0.56	0.47	0.48
Treatment Comparison				

Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.07			
95% CI	(-0.05,0.20)			
p-value	0.2704			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.16			
95% CI	(0.00,0.32)			
p-value	0.0476			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.15			
95% CI	(-0.01,0.31)			
p-value	0.0626			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.08			
95% CI	(-0.08,0.24)			
p-value	0.3211			
[1] Least squares mean from ANCOVA adjusted for subject, period, treatment and baseline covariate.				
[2] Mean difference is the difference in adjusted means.				
Table 7: Summary and Analysis of Summed Backache Intensity Difference - SBID _{0-2, 0-3, 0-4 and 0-6 Hours}				
SBID _{0-2 hours}				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	297	301	150	151
Mean (SD)	0.96 (1.150)	0.82 (1.216)	0.62 (0.974)	0.55 (1.228)
Adjusted Mean ^[1]	0.94	0.81	0.67	0.58
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.14			
95% CI	(-0.01,0.28)			
p-value	0.0664			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.28			
95% CI	(0.09,0.46)			
p-value	0.0034			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.36			
95% CI	(0.18,0.55)			
p-value	0.0001			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.23			
95% CI	(0.04,0.41)			
p-value	0.0161			
SBID _{0-3 hours}				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	297	301	150	151
Mean (SD)	1.79 (1.793)	1.54 (1.928)	1.21 (1.651)	1.10 (2.036)
Adjusted Mean ^[1]	1.76	1.51	1.28	1.17
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.25			
95% CI	(0.03,0.47)			
p-value	0.0245			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.48			
95% CI	(0.20,0.76)			

p-value	0.0007			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.59			
95% CI	(0.31,0.86)			
p-value	< 0.0001			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.34			
95% CI	(0.06,0.61)			
p-value	0.0164			
SBID ₀₋₄ hours				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	297	301	150	151
Mean (SD)	2.65 (2.520)	2.33 (2.660)	1.88 (2.374)	1.72 (2.858)
Adjusted Mean ^[1]	2.62	2.29	1.98	1.83
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.33			
95% CI	(0.04,0.62)			
p-value	0.0260			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.63			
95% CI	(0.27,1.00)			
p-value	0.0008			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.79			
95% CI	(0.42,1.15)			
p-value	< 0.0001			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.46			
95% CI	(0.09,0.83)			
p-value	0.0140			
SBID ₀₋₆ hours				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	297	301	150	151
Mean (SD)	4.40 (3.998)	3.92 (4.253)	3.32 (3.947)	2.90 (4.519)
Adjusted Mean ^[1]	4.34	3.85	3.47	3.11
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.48			
95% CI	(0.06,0.91)			
p-value	0.0255			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.87			
95% CI	(0.33,1.41)			
p-value	0.0017			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	1.23			
95% CI	(0.69,1.77)			
p-value	< 0.0001			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.74			
95% CI	(0.21,1.28)			
p-value	0.0069			

[1] Least squares mean from ANCOVA adjusted for subject, period, treatment and baseline covariate.

[2] Mean difference is the difference in adjusted means.

Table 8: Summary and Analysis of Tiredness Intensity Difference From Baseline at 0.5, 1 and 2 Hours

At 0.5 hours

Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	278	282	143	142
Mean (SD)	0.14 (0.440)	0.11 (0.425)	0.05 (0.417)	0.11 (0.431)
Adjusted Mean ^[1]	0.14	0.10	0.06	0.12

Treatment Comparison

Paracetamol + Caffeine vs. Paracetamol

Mean Difference ^[2]	0.04
95% CI	(-0.03,0.11)
p-value	0.2267

Paracetamol + Caffeine vs. Caffeine

Mean Difference ^[2]	0.08
95% CI	(0.00,0.16)
p-value	0.0473

Paracetamol + Caffeine vs. Placebo

Mean Difference ^[2]	0.02
95% CI	(-0.06,0.10)
p-value	0.6099

Paracetamol vs. Placebo

Mean Difference ^[2]	-0.02
95% CI	(-0.10,0.06)
p-value	0.6391

At 1 hours

Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	278	282	143	142
Mean (SD)	0.33 (0.605)	0.29 (0.580)	0.29 (0.648)	0.30 (0.607)
Adjusted Mean ^[1]	0.33	0.28	0.31	0.32

Treatment Comparison

Paracetamol + Caffeine vs. Paracetamol

Mean Difference ^[2]	0.05
95% CI	(-0.03,0.14)
p-value	0.2262

Paracetamol + Caffeine vs. Caffeine

Mean Difference ^[2]	0.02
95% CI	(-0.09,0.13)
p-value	0.6908

Paracetamol + Caffeine vs. Placebo

Mean Difference ^[2]	0.01
95% CI	(-0.10,0.12)
p-value	0.8416

Paracetamol vs. Placebo

Mean Difference ^[2]	-0.04
95% CI	(-0.15,0.07)
p-value	0.4357

At 2 hours

Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	278	282	143	142
Mean (SD)	0.48 (0.673)	0.38 (0.742)	0.43 (0.737)	0.39 (0.781)
Adjusted Mean ^[1]	0.48	0.36	0.45	0.42

Treatment Comparison

Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.12			
95% CI	(0.02,0.22)			
p-value	0.0221			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.02			
95% CI	(-0.10,0.15)			
p-value	0.7003			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.05			
95% CI	(-0.07,0.18)			
p-value	0.4019			
Paracetamol vs. Placebo				
Mean Difference ^[2]	-0.07			
95% CI	(-0.19,0.06)			
p-value	0.3058			
[1] Least squares mean from ANCOVA adjusted for subject, period, treatment and baseline covariate.				
[2] Mean difference is the difference in adjusted means.				
Table 9: Summary and Analysis of Summed Tiredness Intensity Difference - STID 0-2, 0-3, 0-4 and 0-6 Hours				
STID 0-2 hours				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	278	282	143	142
Mean (SD)	0.71 (1.040)	0.58 (1.097)	0.60 (1.146)	0.60 (1.142)
Adjusted Mean ^[1]	0.71	0.55	0.64	0.64
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.17			
95% CI	(0.01,0.32)			
p-value	0.0321			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.08			
95% CI	(-0.11,0.26)			
p-value	0.4266			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.07			
95% CI	(-0.12,0.26)			
p-value	0.4662			
Paracetamol vs. Placebo				
Mean Difference ^[2]	-0.10			
95% CI	(-0.28,0.09)			
p-value	0.3127			
STID 0-3 hours				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	278	282	143	142
Mean (SD)	1.31 (1.657)	1.15 (1.795)	1.07 (1.788)	1.01 (1.822)
Adjusted Mean ^[1]	1.32	1.08	1.13	1.09
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.23			
95% CI	(0.01,0.46)			
p-value	0.0451			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.18			
95% CI	(-0.10,0.47)			

p-value	0.2081			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.23			
95% CI	(-0.05,0.51)			
p-value	0.1114			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.00			
95% CI	(-0.29,0.28)			
p-value	0.9801			
STID 0-4 hours				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	278	282	143	142
Mean (SD)	1.96 (2.346)	1.80 (2.581)	1.60 (2.566)	1.47 (2.542)
Adjusted Mean ^[1]	1.96	1.69	1.70	1.58
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.27			
95% CI	(-0.04,0.58)			
p-value	0.0930			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.26			
95% CI	(-0.12,0.65)			
p-value	0.1797			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.38			
95% CI	(-0.01,0.77)			
p-value	0.0531			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.12			
95% CI	(-0.27,0.50)			
p-value	0.5569			
STID 0-6 hours				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
n	278	282	143	142
Mean (SD)	3.25 (3.895)	3.09 (4.311)	2.54 (4.182)	2.34 (4.241)
Adjusted Mean ^[1]	3.25	2.91	2.72	2.50
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Mean Difference ^[2]	0.34			
95% CI	(-0.15,0.82)			
p-value	0.1711			
Paracetamol + Caffeine vs. Caffeine				
Mean Difference ^[2]	0.52			
95% CI	(-0.09,1.13)			
p-value	0.0933			
Paracetamol + Caffeine vs. Placebo				
Mean Difference ^[2]	0.75			
95% CI	(0.14,1.35)			
p-value	0.0162			
Paracetamol vs. Placebo				
Mean Difference ^[2]	0.41			
95% CI	(-0.20,1.01)			

p-value	0.1877			
[1] Least squares mean from ANCOVA adjusted for subject, period, treatment and baseline covariate.				
[2] Mean difference is the difference in adjusted means.				
Table 10: Summary and Analysis of Proportion of Subjects Taking Rescue Medication				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
Proportion of Subjects Taking Rescue Medication	0.09	0.11	0.13	0.16
Treatment Comparison				
Paracetamol + Caffeine vs. Paracetamol				
Proportion Difference ^[1]	-0.02			
95% CI	(-0.07,0.02)			
p-value	0.2858			
Paracetamol + Caffeine vs. Caffeine				
Proportion Difference ^[1]	-0.04			
95% CI	(-0.11,0.03)			
p-value	0.2393			
Paracetamol + Caffeine vs. Placebo				
Proportion Difference ^[1]	-0.07			
95% CI	(-0.14,-0.01)			
p-value	0.0278			
Paracetamol vs. Placebo				
Proportion Difference ^[1]	-0.02			
95% CI	(-0.08,0.04)			
p-value	0.5316			
[1] McNemars test				
Safety Results (Safety population, N=320):				
Table 11: Treatment Emergent Adverse Events(AEs)				
Treatments	Paracetamol + Caffeine	Paracetamol	Caffeine	Placebo
Number Of Subjects With AEs Least One AE, n (%)	16 (5.0)	18 (5.6)	6 (3.7)	10 (6.3)
Nervous System Disorders				
Headache	5 (1.6)	6 (1.9)	3 (1.9)	5 (3.2)
Dizziness	3 (0.9)	3 (0.9)	1 (0.6)	1 (0.6)
Dysgeusia	0	0	0	1 (0.6)
Tremor	0	1 (0.3)	0	0
Gastrointestinal Disorders				
Nausea	4 (1.3)	1 (0.3)	2 (1.2)	3 (1.9)
Vomiting	0	2 (0.6)	0	0
Abdominal pain	0	1 (0.3)	0	0
Abdominal pain lower	1 (0.3)	0	0	0
Diarrhoea	0	1 (0.3)	0	0
Epigastric discomfort	0	1 (0.3)	0	0
Infections And Infestations				
Ear infection	0	1 (0.3)	0	1 (0.6)
Cystitis	0	0	0	1 (0.6)
Lower respiratory tract infection	1 (0.3)	0	0	0
Nasopharyngitis	1 (0.3)	0	0	0
Pharyngitis	0	1 (0.3)	0	0
Skin infection	0	1 (0.3)	0	0

General Disorders And Administration Site Condition				
Hangover	1 (0.3)	0	0	0
Influenza like illness	1 (0.3)	0	0	0
Musculoskeletal And Connective Tissue Disorders				
Neck pain	1 (0.3)	0	0	0
Pain in extremity	0	1 (0.3)	0	0
Surgical And Medical Procedures				
Abortion Induced	0	2 (0.6)	0	0
Cardiac Disorders				
Palpitations	1 (0.3)	0	0	0
Immune System Disorders				
Seasonal Allergy	1 (0.3)	0	0	0
Psychiatric Disorders				
Nervousness	1 (0.3)	0	0	0
Respiratory, Thoracic And Mediastinal Disorders				
Pharyngolaryngeal Pain	0	0	1 (0.6)	0
Vascular disorders				
Hot Flush	1 (0.3)	0	0	0
Serious Adverse Events (SAEs) - On-Therapy				
No SAE was reported.				