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 + Caffeine

Study Number: A2260335

Title: A Comparison of Two Analgesic Products for the Treatment of Headache

Rationale: To investigate headache relief of two analgesic test treatments over the time.

Phase: III

Study Period: 01 May 2007 to 30 Nov 2007

Study Design: This was a double-blind, double-dummy, randomized, active and placebo control, three-arm, parallel group study. Subjects were out-patient sufferers of episodic tension-type headaches and were randomly-assigned to treatment in a 3:3:1 ratio with Rapidly Absorbed Paracetamol and Caffeine (RAPC), ibuprofen or placebo, respectively. Subjects were required to attend two clinic visits; a Screening visit (Visit 1) and a follow-up visit (Visit 2). In between the two visits, subjects who subsequently experienced a self-assessed moderate-to-severe episodic tension-type headache treated themselves with assigned study treatment and recorded pain relief scores on a diary card at scheduled time points over the subsequent 4 hours.

Centre: 1, UK

Indication: Pain

Treatments:

Test Products:

1. RAPC (Paracetamol + caffeine 500/65 mg) Tablets, and
2. RAPC placebo tablets

1000mg of paracetamol + 130mg of caffeine (RAPC; two 500mg paracetamol + 65mg caffeine tablets and two Ibuprofen placebo tablets taken as a single dose with a small glass of water).

Reference Products:

1. Ibuprofen 200 mg tablets, and
2. Ibuprofen placebo tablets

400mg of Ibuprofen (two 200mg ibuprofen and two RAPC placebo tablets taken as a single dose with a small glass of water).

Objectives:

Primary objective:

The primary objective of this study was to compare the efficacy of a RAPC tablet versus (vs.) placebo and vs. Ibuprofen tablet in terms of total pain relief over 30 minutes ($TOTPAR_{0\text{-}30\ min}$).

Secondary objectives:

The secondary objectives of the study were to compare the analgesic efficacy of RAPC tablet vs. placebo and vs. Ibuprofen in terms of TOTPAR, over 60, 120, and 240 minutes, pain relief scores at individual time points, time to pain relief, number of headaches resolved, global evaluation, and time to rescue medication and also the frequency of adverse events (AEs).

Primary Outcome Endpoint:

$TOTPAR_{0\text{-}30\ mins}$

Secondary Outcome Endpoints:

1. $TOTPAR_{0\text{-}60\ mins,}$
2. $TOTPAR_{0\text{-}120\ mins,}$
3. $TOTPAR_{0\text{-}240\ mins}$
4. Time to the first assessment at which a subject recorded a score ≥1 for headache pain relief (which is subsequently confirmed by a score of ≥2 on at least two consecutive later assessments of headache pain relief). Subjects not achieving a pain relief score of ≥1 followed by two consecutive pain relief scores of ≥2, or if pain relief is achieved after taking rescue medication, had a censored time set to the duration of the study (4 hours).
5. Time to the first assessment at which a subject recorded a score ≥2 for headache pain relief (followed by a consecutive assessment when the score was ≥2). Subjects not achieving two consecutive pain relief scores of ≥2, or if pain relief is achieved after taking rescue medication, had a censored time set to the duration of

the study (4 hours).

6. Number of headaches resolved at 2 hours. A headache was considered resolved when a pain relief score of 4 is recorded, and all subsequent scores are 4.
7. Pain relief scores - scores at each time point (10, 20, 30, 40, 50 minutes, 1, 1.5, 2, 3 and 4 hours) using a 5-point Verbal Rating Scale (VRS).
8. Time to rescue medication. Subjects not taking rescue medication were censored at the time they withdrew from / completed the study, up to 4 hrs.
9. Global Pain Relief Score (GPRS) at the 4 hr assessment post-dose assessment (or when rescue medication is taken) using a 5-point VRS.

Statistical Methods:

Analysis of covariance was used for TOTPAR, with factors for treatment group and baseline assessment of pain intensity (Verbal Rating Scale score) as a covariate. Treatment differences are presented with 95% confidence intervals (CIs) and an associated p-value. All tests were two-sided and with nominal p-values ≤ 0.05. Time to first assessment when a subject recorded a score ≥ 1 for pain relief and time to first assessment when a subject recorded a score ≥ 2 for pain relief were analyzed using a Cox proportional hazards model from PROC PHREG in Statistical Analysis System (SAS) modeling for treatment group and baseline assessment of pain intensity as a covariate. GPRS analyses were performed based on logistic regression. Number of headaches resolved after 2 hours were analyzed using a chi-square test in Proc freq of SAS.

Study Population:

Subject Disposition

	RAPC Tablets	Ibuprofen	Placebo
Subjects randomized, n	188	189	62
Subjects received test treatment, n	178	175	55
Subjects completed study, n	176	175	55
Subject did not complete the study, n	12	14	7
Lost To Follow-Up	4	7	3
Protocol Deviation	2	0	0
Withdrawal of consent	1	0	0
Other	5	7	4

Demographics	RAPC Tablets (N=188)	Ibuprofen (N=189)	Placebo (N=62)
Sex, n (%)			
Females: Males	138 (73.4): 50 (26.6)	137 (72.5): 52 (27.5)	45 (72.6): 17 (27.4)
Mean Age, years (SD)	23.37 (7.386)	23.77 (7.236)	24.11 (8.319)
Race, n (%)			
Caucasian	174 (92.6)	173 (91.5)	59 (95.2)
Black	1 (0.5)	3 (1.6)	2 (3.2)
Asian	13 (6.9)	13 (6.9)	1 (1.6)

Primary Outcome Results (Intent To Treat [ITT] population)

Table 1: Total Pain Relief 0-30 Minutes

Treatments	RAPC Tablets	Ibuprofen	Placebo
N	178	175	55
Mean (SD)	12.47 (15.89)	11.43 (14.33)	12.55 (15.18)
Median (Minimum[Min.]-Maximum[Max])	10.00 (0.0-90.0)	10.00 (0.0- 70.0)	10.00 (0.0- 70.0)
Adj Mean[1]	12.46	11.43	12.56
Comparison between treatments			
RAPC vs. Ibuprofen			
Treatment difference [2]	1.03		
95% CI	(-2.14, 4.21)		
p-value	0.5229		

RAPC vs. Placebo			
Treatment difference [2]	-0.10		
95% CI	(-4.70, 4.51)		
p-value	0.9674		
Ibuprofen vs. Placebo			
Treatment difference [2]	-1.13		
95% CI	(-5.74, 3.48)		
p-value	0.6305		
[1] Adjusted mean are least squares means from ANCOVA adjusted for baseline pain intensity. *[2] Treatment difference in adjusted means of first named treatment minus second named treatment.*			
Secondary Outcome Results (ITT population)			
Table 2: Total Pain Relief 0-60 Minutes			
Treatments	RAPC Tablets	Ibuprofen	Placebo
N	178	175	55
Mean (SD)	64.16 (42.89)	60.11 (42.05)	58.73 (42.95)
Median (Min.-Max)	60.00 (0- 210.0)	50.00 (0.0- 190.0)	60.00 (0.0-170)
Adj Mean[1]	64.05	60.16	58.96
Comparison between treatments			
RAPC vs. Ibuprofen			
Treatment difference [2]	3.89		
95% CI	(-5.02, 12.80)		
p-value	0.3916		
RAPC vs. Placebo			
Treatment difference [2]	5.09		
95% CI	(-7.84, 18.02)		
p-value	0.4396		
Ibuprofen vs. Placebo			
Treatment difference [2]	1.20		
95% CI	(-11.7, 14.14)		
p-value	0.8554		
[1] Adjusted mean are least squares means from ANCOVA adjusted for baseline pain intensity. *[2] Treatment difference in adjusted means of first named treatment minus second named treatment.*			
Table 3 Total Pain Relief 0-120 Minutes(ITT population)			
Treatments	RAPC Tablets	Ibuprofen	Placebo
N	175	172	52
Mean (SD)	221.60 (100.70)	214.48 (103.81)	215.58 (94.15)
Median (Min.-Max)	220.00 (0.0-450.0)	215.00 (0.0-430.0)	210.00 (0.0-410.0)
Adjusted Mean[1]	221.28	214.61	216.21
Comparison between treatments			
RAPC vs. Ibuprofen			
Treatment difference [2]	6.66		
95% CI	(-14.7, 28.04)		
p-value	0.5405		
RAPC vs. Placebo			
Treatment difference [2]	5.06		
95% CI	(-26.4, 36.53)		
p-value	0.7520		
Ibuprofen vs. Placebo			
Treatment difference [2]	-1.60		
95% CI	(-33.1, 29.90)		
p-value	0.9205		
[1] Adjusted mean are least squares means from ANCOVA adjusted for baseline pain intensity. *[2] Treatment difference in adjusted means of first named treatment minus second named treatment.*			

Table 4 Total Pain Relief 0-240 Minutes (ITT population)			
Treatments	RAPC Tablets	Ibuprofen	Placebo
N	164	157	48
Mean (SD)	628.29 (188.96)	617.52 (190.64)	617.50 (193.98)
Median (Min.-Max)	690.00 (120.0-930.0)	660.00 (180.0-910.0)	645.00 (0.0-890.0)
Adjusted Mean[1]	627.80	617.34	619.76
Comparison between treatments			
RAPC vs. Ibuprofen			
Treatment difference [2]	10.46		
95% CI	(-31.3, 52.23)		
p-value	0.6226		
RAPC vs. Placebo			
Treatment difference [2]	8.04		
95% CI	(-53.5, 69.59)		
p-value	0.7973		
Ibuprofen vs. Placebo			
Treatment difference [2]	-2.42		
95% CI	(-64.2, 59.40)		
p-value	0.9387		

[1] Adjusted mean are least squares means from ANCOVA adjusted for baseline pain intensity.
[2] Treatment difference in adjusted means of first named treatment minus second named treatment.

Table 5 Pain Relief Scores Over Time (ITT population)					
RAPC Time points, (N=178)	10 mins	20 mins	30 mins	40 mins	50 mins
N	178	178	178	178	178
Mean (SD)	0.10 (0.370)	0.35 (0.631)	0.80 (0.853)	1.36 (1.006)	1.70 (1.077)
Median (Min.-Max)	0.00 (0.0-2.0)	0.00 (0.0-3.0)	1.00 (0.0-4.0)	1.00 (0.0-4.0)	2.00 (0.0-4.0)
Adjusted Mean[1]	0.10	0.35	0.80	1.36	1.70
RAPC Time points (N=178)	60 mins	90 mins	120 mins	180 mins	240 mins
N	178	177	174	165	163
Mean (SD)	2.11 (1.157)	2.45 (1.143)	2.78 (1.152)	3.19 (1.023)	3.42 (0.936)
Median (Min.- Max)	2.00 (0.0-4.0)	3.00 (0.0-4.0)	3.00 (0.0-4.0)	4.00 (0.0-4.0)	4.00 (0.0-4.0)
Adjusted Mean[1]	2.10	2.44	2.78	3.19	3.42
Ibuprofen Time points (N=175)	10 mins	20 mins	30 mins	40 mins	50 mins
N	175	175	175	175	175
Mean (SD)	0.09 (0.337)	0.31 (0.556)	0.74 (0.786)	1.26 (1.000)	1.65 (1.119)
Median (Min.-Max)	0.00 (0.0-2.0)	0.00 (0.0-2.0)	1.00 (0.0-3.0)	1.00 (0.0-4.0)	2.00 (0.0-4.0)
Adjusted Mean[1]	0.09	0.31	0.74	1.26	1.65
Ibuprofen Time points (N=175)	60 mins	90 mins	120 mins	180 mins	240 mins
N	175	175	172	162	157
Mean (SD)	1.96 (1.176)	2.35 (1.189)	2.73 (1.200)	3.16 (1.045)	3.32 (1.000)
Median (Min.-Max)	2.00 (0.0-4.0)	2.00 (0.0-4.0)	3.00 (0.0-4.0)	4.00 (0.0-4.0)	4.00 (0.0-4.0)
Adjusted Mean[1]	1.96	2.36	2.73	3.16	3.32
Placebo Time points (N=55)	10 mins	20 mins	30 mins	40 mins	50 mins
N	55	55	55	55	55
Mean (SD)	0.11 (0.369)	0.25 (0.552)	0.89 (0.854)	1.07 (0.997)	1.56 (1.085)

Median (Min.-Max)	0.00 (0.0-2.0)	0.00 (0.0-3.0)	1.00 (0.0-3.0)	1.00 (0.0-4.0)	2.00 (0.0-4.0)
Adjusted Mean[1]	0.11	0.26	0.89	1.08	1.57
Placebo Time points (N=55)	60 mins	90 mins	120 mins	180 mins	240 mins
N	55	55	52	49	48
Mean (SD)	1.98 (1.254)	2.24 (1.186)	2.75 (1.046)	3.22 (1.026)	3.35 (1.082)
Median (Min.-Max)	2.00 (0.0-4.0)	2.00 (0.0-4.0)	3.00 (0.0-4.0)	4.00 (0.0-4.0)	4.00 (0.0-4.0)
Adjusted Mean[1]	1.99	2.24	2.76	3.24	3.37
Treatment Comparisons					
RAPC vs. Ibuprofen	10 mins	20 mins	30 mins	40 mins	50 mins
Treatment difference [2]	0.02	0.03	0.05	0.09	0.05
95% CI	-0.06,0.09	-0.09,0.16	-0.12,0.23	-0.12,0.30	-0.18,0.28
p-value	0.6621	0.6127	0.5329	0.3810	0.6487
RAPC vs. Ibuprofen	60 mins	90 mins	120 mins	180 mins	240 mins
Treatment difference [2]	0.14	0.09	0.05	0.03	0.10
95% CI	-0.11,0.39	-0.16,0.33	-0.20,0.29	-0.19,0.26	-0.11,0.32
p-value	0.2697	0.4847	0.6921	0.7870	0.3494
RAPC vs. Placebo	10 mins	20 mins	30 mins	40 mins	50 mins
Treatment difference [2]	-0.01	0.09	-0.09	0.28	0.13
95% CI	-0.11,0.10	-0.09,0.27	-0.34,0.16	-0.02,0.58	-0.20,0.46
p-value	0.9224	0.3299	0.4662	0.0714	0.4387
RAPC vs. Placebo	60 mins	90 mins	120 mins	180 mins	240 mins
Treatment difference [2]	0.11	0.20	0.02	-0.05	0.05
95% CI	-0.25,0.46	-0.16,0.56	-0.34,0.38	-0.38,0.28	-0.26,0.37
p-value	0.5571	0.2706	0.9109	0.7831	0.7383
Ibuprofen vs. Placebo	10 mins	20 mins	30 mins	40 mins	50 mins
Treatment difference [2]	-0.02	0.06	-0.15	0.19	0.08
95% CI	-0.13,0.09	-0.12,0.24	-0.40,0.10	-0.12,0.49	-0.26,0.41
p-value	0.6903	0.5317	0.2472	0.2299	0.6453
Ibuprofen vs. Placebo	60 mins	90 mins	120 mins	180 mins	240 mins
Treatment difference [2]	-0.03	0.11	-0.03	-0.08	-0.05
95% CI	-0.39,0.33	-0.24,0.47	-0.39,0.33	-0.41,0.25	-0.37,0.27
p-value	0.8619	0.5350	0.8750	0.6471	0.7637

[1] Adjusted mean are least squares means from ANCOVA adjusted for baseline intensity.
[2] Treatment Difference is difference in adjusted means of first named treatment minus second named treatment.

Table 6 Time (minutes) To First Assessment When A Subject Recorded A score >= 1 For Pain Relief

	RAPC Tablets	Ibuprofen	Placebo
Achieved			
Yes	173 (97.2)	168 (96.0)	51 (92.7)
No	5 (2.8)	7 (4.0)	4 (7.3)
N	173	168	51
Mean (SD)	36.71 (27.325)	37.20 (25.965)	38.04 (24.333)
Median (Min.-Max)	30.00 (10.0-180.0)	30.00 (10.0-180.0)	30.00 (10.0-120.0)
Treatment Comparison			
RAPC vs. Ibuprofen			
Hazard Ratio [1]	1.177		
95% CI	(0.860, 1.610)		
p-value	0.3090		
RAPC vs. Placebo			
Hazard Ratio [1]	1.049		
95% CI	(0.848, 1.298)		
p-value	0.6571		
Ibuprofen vs. Placebo			

Hazard Ratio [1]	0.953		
95% CI	(0.771, 1.179)		
p-value	0.6571		
[1] Hazard ratio from proportional hazards model adjusting for baseline pain intensity such that a hazard ratio > 1 indicatesthat there is a greater chance of the event occuring with the first named treatment.			
Table 7 Time (minutes) To First Assessment When A Subject Recorded A score >= 2 For Pain Relief			
	RAPC Tablets	Ibuprofen	Placebo
Achieved			
Yes	164 (92.1)	159 (90.9)	48 (87.3)
No	14 (7.9)	16 (9.1)	7 (12.7)
N	164	159	48
Mean (SD)	62.07 (43.278)	66.54 (46.224)	58.54 (38.426)
Median (Minimum[Min.]-Maximum[Max])	50.00 (10.0-240.0)	50.00 (10.0-240.0)	50.00 (10.0-240.0)
Treatment Comparison			
RAPC vs. Ibuprofen			
Hazard Ratio [1]	1.091		
95% CI	(0.790, 1.505)		
p-value	0.5976		
RAPC vs. Placebo			
Hazard Ratio [1]	1.095		
95% CI	(0.880, 1.362)		
p-value	0.4161		
Ibuprofen vs. Placebo			
Hazard Ratio [1]	0.913		
95% CI	(0.734, 1.136)		
p-value	0.4161		
[1] Hazard ratio from proportional hazards model adjusting for baseline pain intensity such that a hazard ratio > 1 indicatesthat there is a greater chance of the event occurring with the first named treatment.			
Table 8 Global Pain Relief Score (GPRS) Assessment			
Global Pain Relief Score	RAPC Tablets (N=178) N (%)	Ibuprofen (N=175) N (%)	
Poor/Fair/Good	124 (70.1)	136 (77.7)	
Very Good/Excellent	53 (29.9)	39 (22.3)	
Odds Ratio	1.467		
95% CI	(0.906, 2.375)		
p-value	0.1193		
Table 8 Number of Headaches Resolved at 2 Hours			
Pain Relief	RAPC Tablets (N=178) N (%)	Ibuprofen (N=175) N (%)	
Resolved	58 (33.3)	61 (35.5)	
Not resolved	116 (66.7)	111 (64.5)	
Chi square	0.1742		
Prob.	0.6764		
Table 9 Time to Rescue Medication			
	RAPC Tablets (N=178)	Ibuprofen (N=175)	Placebo (N=55)
N	14	21	8
Mean (SD)	146.79 (43.853)	178.24 (52.434)	156.25 (62.264)
Median (Min.-Max)	137.00 (65.0-240.0)	173.00 (120.0-270.0)	127.50 (120.0-300.0)
Safety Results			

Table 10 Treatment Emergent Adverse Events (AEs) (Safety population):			
	RAPC Tablets (N=178) n (%)	Ibuprofen (N=175) n (%)	Placebo (N=55) n (%)
Number Of Subjects With At Least One AE	29 (16.3)	12 (6.9)	6 (10.9)
Gastrointestinal Disorders			
Nausea	13 (7.3)	5 (2.9)	2 (3.6)
Eructation	3 (1.7)	0	0
Abdominal pain	2 (1.1)	0	0
Dry mouth	2 (1.1)	0	0
Abdominal pain upper	0	0	1 (1.8)
Diarrhoea	1 (0.6)	0	0
Epigastric discomfort	0	1 (0.6)	0
Stomatitis	1 (0.6)	0	0
Vomiting	1 (0.6)	0	0
Nervous System Disorders			
Disturbance in attention	1 (0.6)	2 (1.1)	0
Dizziness	2 (1.1)	0	0
Psychomotor hyperactivity	1 (0.6)	1 (0.6)	0
Somnolence	1 (0.6)	0	1 (1.8)
Lethargy	0	1 (0.6)	0
Paraesthesia	1 (0.6)	0	0
Poor quality sleep	1 (0.6)	0	0
General Disorders And Administration Site Conditions			
Thirst	1 (0.6)	1 (0.6)	0
Asthenia	0	0	1 (1.8)
Energy increased	1 (0.6)	0	0
Fatigue	1 (0.6)	0	0
Eye Disorders			
Eye Pain	0	0	1 (1.8)
Vision Blurred	1 (0.6)	0	0
Musculoskeletal And Connective Tissue Disorders			
Neck pain	0	1 (0.6)	0
Pain in jaw	1 (0.6)	0	0
Psychiatric Disorders			
Anxiety	1 (0.6)	0	0
Insomnia	1 (0.6)	0	0
Vascular Disorders			
Hot Flush	1 (0.6)	0	1 (1.8)
Cardiac Disorders			
Palpitations	1 (0.6)	0	0
Respiratory, Thoracic And Mediastinal Disorders			
Dry Throat	0	1 (0.6)	0
Serious Adverse Events (SAEs) - On-Therapy			
No SAE's were reported.			