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 Theobromine

Study Number: A2720382

Title: A Proof-of-Principle Analgesic Adjuvant Pilot Study in Post-Operative Dental Pain

Rationale: To investigate whether theobromine has any clinical adjuvant analgesic activity in combination with paracetamol by observing the effect of paracetamol 1 g plus theobromine 600 mg compared to paracetamol 1 g alone.

Phase: II

Study Period: 23rd Oct 2007 to 16th Sept 2008

Study Design: This was a single centre, double blind, randomised, single dose, two arm, parallel group study in subjects who experience moderate to severe pain (demonstrated using a Verbal Rating Scale [VRS] and confirmed by Visual Analogue Scale [VAS] score) after undergoing surgical removal of one partial or fully impacted lower third molar under local anaesthetic.

Centre: 1 in United Kingdom

Indication: Pain

Treatments:

Test Products:

1. Theobromine powder 600 mg,
2. Paracetamol Tablets (500 mg × 2 = 1 g),
3. Sucralose 100 mg, and
4. Sterile water 400 mL.

Paracetamol (2 tablets) was taken orally with Theobromine (600 mg) dissolved in 400 mL of tepid water (containing 100 mg of sucralose).

Reference Products:

1. Paracetamol (500 mg × 2 = 1 g),
2. Sucralose 100 mg, and
3. Sterile water 400 mL.

Paracetamol (2 tablets) was taken orally with 400 mL of tepid water (containing 100 mg of sucralose).

Objectives:

Primary Objective:

To compare the analgesic efficacy of Theobromine + Paracetamol versus (vs.) Paracetamol alone.

Secondary Objectives:

1. To summarise pharmacokinetic (PK) data (area under the plasma concentration-time curve from zero to 6 hours [$AUC_{0\text{-}6\ hrs}$], maximum plasma concentration [C_{max}], time to maximum plasma concentration [t_{max}]) for Theobromine and for Paracetamol (alone and in combination with Theobromine).
2. To summarise the frequency of micturation for Theobromine + Paracetamol and for Paracetamol alone.
3. To summarise safety data for Theobromine + Paracetamol and for Paracetamol alone.

Primary Outcome Endpoint:

Total Pain Relief (TOTPAR) at 1, 2, 4 and 6 hrs: $TOTPAR = \Sigma(R_t \times (time_t - time_{t-1}))$, where R_t = pain relief score at time t, and $time_t$ = time in hours.

Secondary Outcome Endpoints:

1. Pain relief score (PRS) at 15, 30, 45, 60, 120, 180 and 360 minutes, subjects were scored on a score of 0-4, were 0 =no relief, 1 = a little relief, 2 = some relief, 3 = a lot of relief and 4 = complete relief.
2. Global pain relief score at the 6 hr assessment period (or when rescue medication is taken) using a 5-point categorical scale, where 0 = poor, 1 = fair, 2 = good, 3 = very good and 4 = excellent.
3. Time to rescue medication.
4. Micturation data (frequency)
5. $AUC_{0\text{-}6\ hours}$ (µg*h/mL): area under the plasma concentration-time curve from zero to 6 hours
6. C_{max} (µg/mL) – maximum plasma concentration
7. T_{max} (hours) - time to maximum plasma concentration

Statistical Methods:
Analysis of covariance was used to analyse TOTPAR, with factor for treatment group and baseline assessment of pain intensity (VAS score) as a covariate where as analysis of variance was used to analyze PRS (change from baseline), with factor for treatment group. Treatment differences were presented with 95% confidence intervals (CIs) and an associated p-value. Global pain relief scores were analysed using the chi square test. Time to rescue medication was compared using a Log-Rank test. All statistical testing was performed at the two-sided 5% level of significance. Micturation data were summarized by frequency for each treatment group. PK endpoints and plasma concentration levels were summarized by means of descriptive statistics (mean, standard, median, minimum and maximum).

Study Population:

Subject Disposition

	Overall
Subjects Randomized, n	102
Subjects completed study, n	100
Subject did not complete the study, n	2
Reason for not completing the study, n	
Protocol Deviation	1
Other	1

Demographics (All Subjects Randomized)	Overall
N	102
Sex, n (%)	
Female: Male	66 (64.7): 36 (35.3)
Mean Age, years (SD)	28.39 (7.018)
Race, n (%)	
Caucasian	97 (95.1)
Black	1 (1.0)
Asian	4 (3.9)

Primary Outcome Results (Intent to Treat [ITT] population N=102):

Table 1: Total Pain Relief (TOTPAR) at 1, 2, 4 and 6 hrs

At 1 hrs		
Treatments	Theobromine + Paracetamol	Paracetamol
n	50	52
Mean (SD)	1.73 (0.750)	1.65 (0.908)
LS Mean	1.73	1.64
Treatment comparison		
Theobromine + Paracetamol vs. Paracetamol		
Difference[1]	0.09	
95% CI	-0.23, 0.42	
p-value	0.5823	

At 2 hrs		
Treatments	Theobromine + Paracetamol	Paracetamol
n	50	52
Mean (SD)	3.19 (1.824)	2.92 (1.790)
LS Mean	3.19	2.91
Treatment comparison		
Theobromine + Paracetamol vs. Paracetamol		
Difference[1]	0.28	
95% CI	-0.43, 0.99	
p-value	0.4385	

At 4 hrs		
Treatments	Theobromine + Paracetamol	Paracetamol
n	50	52
Mean (SD)	4.01 (3.055)	4.13 (3.465)
LS Mean	4.00	4.14

Treatment comparison		
Theobromine + Paracetamol vs. Paracetamol		
Difference[1]	-0.14	
95% CI	-1.43, 1.15	
p-value	0.8305	
At 6 hrs		
Treatments	Theobromine + Paracetamol	Paracetamol
n	50	52
Mean (SD)	4.15 (3.618)	4.58 (4.421)
LS Mean	4.13	4.59
Treatment comparison		
Theobromine + Paracetamol vs. Paracetamol		
Difference[1]	-0.46	
95% CI	-2.06, 1.14	
p-value	0.5677	
[1] A Positive difference favors the first named treatment.		
Secondary Outcome Results (ITT Population, N=102)		
Table 2: Pain relief score (PRS)[1] at 15, 30, 45, 60, 120, 180 and 360 minutes		
At 15 minutes		
Treatments	Theobromine + Paracetamol	Paracetamol
n	50	52
Mean (SD)	0.52 (0.735)	0.94 (1.018)
LS Mean	0.52	0.94
Treatment comparison		
Difference[2]	-0.42	
95% CI	-0.77, -0.07	
p-value	0.0185	
At 30 minutes		
Treatments	Theobromine + Paracetamol	Paracetamol
n	50	52
Mean (SD)	1.70 (1.093)	1.69 (1.130)
LS Mean	1.70	1.69
Treatment comparison		
Difference[2]	0.01	
95% CI	-0.43, 0.44	
p-value	0.9722	
At 45 minutes		
Treatments	Theobromine + Paracetamol	Paracetamol
n	50	52
Mean (SD)	2.32 (0.957)	2.04 (1.137)
LS Mean	2.32	2.04
Treatment comparison		
Difference[2]	0.28	
95% CI	-0.13, 0.70	
p-value	0.1799	
At 60 minutes		
Treatments	Theobromine + Paracetamol	Paracetamol
n	49	52
Mean (SD)	2.41 (0.934)	1.94 (1.074)
LS Mean	2.41	1.94
Treatment comparison		
Difference[2]	0.47	
95% CI	0.07, 0.86	
p-value	0.0224	

At 120 minutes		
Treatments	Theobromine + Paracetamol	Paracetamol
n	34	32
Mean (SD)	2.15 (1.105)	2.06 (1.014)
LS Mean	2.15	2.06
Treatment comparison		
Difference[2]	0.08	
95% CI	-0.44, 0.61	
p-value	0.7475	
At 180 minutes		
Treatments	Theobromine + Paracetamol	Paracetamol
n	18	16
Mean (SD)	1.83 (1.295)	2.13 (0.885)
At 360 minutes		
n	1	5
Mean (SD)	3.00 (0)	2.00 (1.000)
[1] Pain relief scores are the difference of pain relief score at the end of each treatment with the respective baseline. *[2] A Positive difference favors the first named treatment.*		
Table 3: Global pain relief score at the 6 hr		
Treatments	Theobromine + Paracetamol	Paracetamol
Poor/Fair/Good		
n (%)	34 (68.0)	33 (63.5)
Very Good/Excellent		
n (%)	16 (32.0)	19 (36.5)
Treatment comparison		
Theobromine + Paracetamol vs. Paracetamol		
Chi Square Test For Proportions		
p-value	0.6294	
Table 4: Time to Rescue Medication		
Treatments	Theobromine + Paracetamol	Paracetamol
n	50	52
Mean (SD)	161.42 (66.573)	166.50 (94.424)
Median (Min.-Max.)	137.50 (65.0-360.0)	138.50 (67.0-360.0)
Treatment comparison		
Theobromine + Paracetamol vs. Paracetamol		
Chi Square Test For Log-Rank		
p-value	0.3834	
Table 5: Frequency Distribution of Micturation Data		
1 Hour Post Dose		
Treatments	Theobromine + Paracetamol	Paracetamol
Number of times subject urinated=0, n (%)	166 (83.00)	189 (90.87)
Number of times subject urinated=1, n (%)	34 (17.00)	19 (9.13)
2 Hour Post Dose		
Treatments	Theobromine + Paracetamol	Paracetamol
Number of times subject urinated=0, n (%)	29 (58.00)	35 (67.31)
Number of times subject urinated=1, n (%)	21 (42.00)	17 (32.69)
3 To 6 Hours Post Dose		
Treatments	Theobromine + Paracetamol	Paracetamol
Number of times subject urinated=0, n (%)	139 (69.50)	155 (75.24)
Number of times subject urinated=1, n (%)	61 (30.50)	50 (24.27)
Number of times subject urinated=2, n (%)	N/A	1 (0.49)
Table 6: $AUC_{0\text{-}6\ hrs}$ **(µg*h/mL)** of Theobromine and Paracetamol		
Theobromine		

Treatments	Theobromine + Paracetamol	Paracetamol
n	48	0
Mean (SD)	57.67 (12.721)	0 (0)
Paracetamol		
Treatments	Theobromine + Paracetamol	Paracetamol
n	50	52
Mean (SD)	34.37 (11.001)	32.65 (8.499)
Table 7: C_{max} **(µg/mL)** of Theobromine and Paracetamol		
Theobromine		
Treatments	Theobromine + Paracetamol	Paracetamol
n	50	9
Mean (SD)	13.50 (2.968)	1.89 (0.604)
Paracetamol		
Treatments	Theobromine + Paracetamol	Paracetamol
n	50	52
Mean (SD)	13.27 (4.667)	11.71 (3.476)
Table 8: T_{max} (hrs) of Theobromine and Paracetamol		
Theobromine		
Treatments	Theobromine + Paracetamol	Paracetamol
n	50	9
Median (Min.-Max.)	1.00 (0.5-6.0)	1.00 (1.0-1.0)
Paracetamol		
Treatments	Theobromine + Paracetamol	Paracetamol
n	50	52
Median (Min.-Max.)	1.00 (0.5-2.0)	1.00 (0.5-3.0)
Safety Results (Safety population, N=102):		
Table 9: Number of Subjects With Treatment Emergent Adverse Events (AEs)		
Treatments	Theobromine + Paracetamol	Paracetamol
n	50	52
Number of subjects with at least one AE, n (%)	12 (24.0)	10 (19.2)
Gastrointestinal Disorders		
Paraesthesia oral	1 (2.0)	2 (3.8)
Nausea	0	2 (3.8)
Toothache	1 (2.0)	1 (1.9)
Oedema mouth	0	1 (1.9)
Oral pain	1 (2.0)	0
Pericoronitis	1 (2.0)	0
Tongue ulceration	1 (2.0)	0
Tooth socket haemorrhage	0	1 (1.9)
Vomiting	1 (2.0)	0
Infections And Infestations		
Post procedural infection	4 (8.0)	3 (5.8)
Tooth infection	2 (4.0)	1 (1.9)
Nervous System Disorders		
Dizziness	0	1 (1.9)
Headache	1 (2.0)	0
Neuropathy peripheral	1 (2.0)	0
Paraesthesia	1 (2.0)	0
Musculoskeletal And Connective Tissue Disorders		
Trismus	1 (2.0)	1 (1.9)

Blood And Lymphatic System Disorders		
Lymphadenopathy	0	1 (1.9)
General Disorders And Administration Site		
Pyrexia	1 (2.0)	0
Serious Adverse Events (SAEs) - On-Therapy		
No SAE was reported.		