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<b>GSK Medicine:</b> Paracetamol and dextromethorphan
<b>Study Number:</b> A2350325
<b>Title:</b> A Proof-of-Principle Clinical Study to Investigate the Efficacy of a Combination Treatment on Single and Repeated Nociceptive Stimuli
<b>Rationale:</b> Paracetamol and dextromethorphan was investigated in comparison to paracetamol alone in order to determine if dextromethorphan has any adjuvant analgesic activity in combination with paracetamol. It was hypothesised that this combination would result in an enhanced analgesic effect compared to paracetamol alone.
<b>Phase:</b> I
<b>Study Period:</b> 31st January 2005 to 16th June 2005
<b>Study Design:</b> This was a single centre, double-blind, randomised, three-way crossover, proof of- principle study conducted in normal, healthy adult subjects (males and females). Experimental tests included electrical stimulation to skin and muscle (single and repeated stimulation); mechanical pressure applied to the muscle and intra-muscular saline to induce referred cutaneous hyperalgesia. Pain assessments were determined pre- and post-dose. Subjects were screened and underwent training/familiarisation in the experimental tests within 14 days of the initial treatment visit. They then returned for three treatment visits, each separated by a minimum of 3 days and a maximum of 10 days. On each treatment day, subjects had fasted for 3 hours prior to dosing and were not allowed fluid intake for 1 hour prior to and 2 hours post-dosing. One hour prior to dosing, subjects received verbal familiarisation of the experimental tests. Baseline experimental tests commenced at 30 minutes ( $\pm 5$ mins) prior to dosing. Following dosing with the assigned study treatment, experimental tests commenced at 1, 2, and 3 hours post-dose (all $\pm 5$ mins). A follow-up visit was performed at the end of treatment visit 3.
<b>Centre:</b> 1 in Denmark (Europe)
<b>Indication:</b> Pain
<b>Treatments:</b> <b>Test Product:</b> <b>Paracetamol 1 g + Dextromethorphan 30 mg:</b> Two paracetamol tablets (1g paracetamol) plus one dextromethorphan tablet (30mg dextromethorphan) taken orally with 150mL of water.
<b>Reference Products:</b> <ol style="list-style-type: none"> <li><b>Paracetamol 1g + Dextromethorphan placebo:</b> Two paracetamol tablets (1g paracetamol) plus one dextromethorphan placebo tablet taken orally with 150mL water.</li> <li><b>Paracetamol placebo + Dextromethorphan placebo:</b> Two paracetamol placebo tablets plus one dextromethorphan placebo tablet taken orally with 150mL water.</li> </ol>
<b>Objectives:</b>  <b>Primary objective:</b> To assess the effect of paracetamol and dextromethorphan compared to paracetamol alone on single and repeated nociceptive stimuli over time.
<b>Secondary Objectives:</b> <ol style="list-style-type: none"> <li>To assess the effect of paracetamol and dextromethorphan compared to placebo on single and repeated nociceptive stimuli over time.</li> <li>To assess the effect of paracetamol compared to placebo on single and repeated nociceptive stimuli over time.</li> <li>To assess the safety of paracetamol and dextromethorphan compared to paracetamol alone and to placebo, as assessed by the incidence and severity of adverse events (AEs).</li> </ol>
<b>Primary Outcome Endpoints:</b> <ol style="list-style-type: none"> <li>Temporal summation pain detection threshold (tsPDT) to electrical skin stimulation at 1, 2 and 3 hours.</li> <li>Area under the stimulus-response curve (at 1, 2 and 3 hours) to repeated electrical skin stimulation.</li> </ol>
<b>Secondary Outcome Endpoints:</b> <ol style="list-style-type: none"> <li>Temporal summation pain detection threshold (tsPDT) to electrical muscle stimulation at 1, 2 and 3 hours.</li> <li>Area under the stimulus-response curve (AUC) (at 1, 2 and 3 hours) to repeated electrical muscle stimulation.</li> <li>Single stimulus pain detection threshold (ssPDT) to electrical stimulation, at 1, 2 and 3 hours.</li> </ol>

4. Single stimulus pain detection threshold to muscle stimulation, at 1, 2 and 3 hours.			
5. Area under the stimulus-response curve (at 1, 2 and 3 hours) to single electrical stimulation.			
6. Area under the stimulus-response curve (at 1, 2 and 3 hours) to single muscle stimulation.			
7. Build up and after-sensation to a 10 sec 20 Hz stimulation (to skin and to muscle)			
8. Build up and after-sensation to a10 sec 2 Hz stimulation (to skin and to muscle)			
9. Pressure Pain Threshold (PPT)			
10. Pressure Pain Tolerance Threshold (PPT-tol): The PPT-tol was defined as the maximal intensity the subject has accepted.			
11. Assessment of muscle pain following intra-muscular injection of hypertonic saline			
12. Vaso-motor response to standardised cutaneous heating.			
<b>Statistical Methods:</b>			
For the primary efficacy variables (temporal summation pain detection threshold, and area under the stimulus-response curve to repeated electrical skin stimulation), it was planned to analyse these using an analysis of covariance model, with baseline as a covariate. After inspection of the data, it was apparent that the data were not normally distributed, and so the Wilcoxon signed rank test was used to analyse the primary efficacy variables. To take into account any baseline differences, the change from baseline rather than the absolute value was used as the endpoint for analysis. The Hodges-Lehmann method was used to construct 95% confidence intervals (CIs) for treatment differences. All statistical testing was two-sided at the 5% significance level. All secondary variables were analysed in the same way as the primary variables.			
<b>Study Population:</b>			
<b>Subject Disposition</b>			
	<b>Overall</b>		
Subjects Randomized, n	20		
Number of subjects in safety population, n	20		
Number of subjects in intent to treat (ITT) population, n	20		
Number of ITT Subjects Not Completing Study, n	2		
Adverse event (Urticarial rash on the right arm and abdomen following administration of placebo)	1		
Other	1		
<b>Demographics (All Randomized Subjects)</b>			
	<b>Overall</b>		
N	20		
<b>Sex, n (%)</b>			
Female: Male	8 (40.0): 12 (60.0)		
<b>Mean Age, years (SD)</b>	25.09 (1.609)		
<b>Race, n (%)</b>			
Caucasian	20 (100.0)		
<b>Primary Outcome Results (ITT population N=20):</b>			
<b>Table 1: Summary Of Temporal Summation Pain Detection Threshold (tsPDT) To Electrical Skin Stimulation (mA)</b>			
<b>Treatments</b>	<b>Paracetamol + Dextromethorphan</b>	<b>Paracetamol</b>	<b>Placebo</b>
<b>At Baseline</b>			
n	19	19	19
Mean (SD)	4.79 (1.483)	4.45 (1.514)	4.85 (1.584)
Median (Minimum [Min], Maximum [Max])	4.70 (2.0, 7.2)	4.00 (2.2, 7.5)	5.00 (1.5, 7.8)
<b>Change from Baseline at 1 hour</b>			
n	19	19	19
Mean (SD)	0.27 (0.370)	0.36 (0.489)	0.17 (0.681)
Median (Min, Max)	0.20 (-0.6, 1.0)	0.40 (-0.4, 1.7)	0.10 (-1.6, 1.3)
<b>Treatment comparison</b>			
<b>Paracetamol + Dextromethorphan versus (vs.) Paracetamol</b>			
Median Difference <sup>[1]</sup>	-0.15		
95% CI	-0.40,0.20		
p-value	0.4002		

Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	0.15		
95% CI	-0.25,0.50		
p-value	0.3851		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	0.20		
95% CI	-0.20,0.60		
p-value	0.2895		
Change from Baseline at 2 hour			
n	19	19	18
Mean (SD)	0.50 (0.814)	0.42 (0.712)	0.43 (0.736)
Median (Min, Max)	0.50 (-1.5, 2.5)	0.30 (-0.9, 1.5)	0.25 (-0.7, 2.6)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	0.00		
95% CI	-0.55,0.65		
p-value	1.0000		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.10		
95% CI	-0.50,0.55		
p-value	0.7908		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	-0.05		
95% CI	-0.50,0.40		
p-value	0.9237		
Change from Baseline at 3 hour			
n	19	19	18
Mean (SD)	0.64 (0.666)	0.69 (1.118)	0.73 (0.782)
Median (Min, Max)	1.00 (-0.5, 1.5)	0.50 (-1.4, 3.2)	0.50 (-0.5, 2.8)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	0.00		
95% CI	-0.70,0.50		
p-value	0.9917		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.10		
95% CI	-0.45,0.30		
p-value	0.4490		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	-0.05		
95% CI	-0.75,0.70		
p-value	0.9540		
[1] Wilcoxon Signed Rank Test. Median difference expressed as first named treatment minus second named treatment.			
Table 2: Summary of Area Under the Stimulus-Response Curve To Repeated Electrical Skin Stimulation (cm*mA)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	19	19	19
Mean (SD)	2.75 (1.400)	2.74 (1.406)	2.67 (1.291)
Median (Min, Max)	3.09 (0.2, 5.5)	2.89 (0.1, 5.5)	2.71 (0.1, 5.5)
Change from baseline at 1 hour			
n	19	19	19
Mean (SD)	-0.09 (0.425)	-0.14 (0.445)	-0.05 (0.470)
Median (Min, Max)	0.04 (-1.0, 0.6)	0.01 (-1.0, 0.8)	-0.08 (-0.9, 0.8)

Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	0.04		
95% CI	-0.25,0.33		
p-value	0.7381		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.06		
95% CI	-0.34,0.21		
p-value	0.4951		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	-0.13		
95% CI	-0.43,0.24		
p-value	0.5721		
Change from baseline at 2 hour			
n	19	19	18
Mean (SD)	-0.20 (0.454)	-0.12 (0.461)	0.04 (0.307)
Median (Min, Max)	-0.11 (-1.4, 0.5)	-0.15 (-1.0, 0.9)	0.08 (-0.5, 0.7)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-0.06		
95% CI	-0.33,0.20		
p-value	0.7983		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.18		
95% CI	-0.49,0.09		
p-value	0.2330		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	-0.14		
95% CI	-0.42,0.16		
p-value	0.2645		
Change from baseline at 3 hour			
n	19	19	18
Mean (SD)	-0.29 (0.523)	-0.18 (0.530)	-0.15 (0.507)
Median (Min, Max)	-0.21 (-1.3, 0.3)	-0.15 (-1.2, 1.0)	-0.04 (-1.2, 0.9)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-0.06		
95% CI	-0.48,0.28		
p-value	0.7680		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.04		
95% CI	-0.43,0.14		
p-value	0.6783		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	-0.07		
95% CI	-0.48,0.43		
p-value	0.7660		
[1] Wilcoxon Signed Rank Test. Median difference expressed as first named treatment minus second named treatment.			
Secondary Outcome Results (ITT population N=20):			
Table 3: Summary of Temporal Summation Pain Detection Threshold (tsPDT) to Electrical Muscle Stimulation (mA)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			

n	19	19	18
Mean (SD)	1.63 (1.360)	1.84 (1.656)	1.82 (1.942)
Median (Min, Max)	1.10 (0.5, 5.2)	1.10 (0.5, 6.2)	1.00 (0.5, 7.3)
Change from Baseline at 1 hour			
n	18	19	17
Mean (SD)	0.02 (0.527)	0.45 (1.208)	0.29 (1.058)
Median (Min, Max)	0.10 (-1.0, 1.0)	0.10 (-0.4, 5.2)	0.00 (-0.9, 4.1)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-0.30		
95% CI	-0.65,0.05		
p-value	0.1066		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.05		
95% CI	-0.55,0.20		
p-value	0.4160		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	0.15		
95% CI	-0.15,0.55		
p-value	0.3334		
Change from Baseline at 2 hour			
n	18	19	16
Mean (SD)	0.20 (0.596)	0.55 (1.193)	0.60 (1.245)
Median (Min, Max)	0.15 (-0.8, 1.5)	0.30 (-0.7, 5.1)	0.20 (-0.7, 4.7)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-0.20		
95% CI	-0.60,0.10		
p-value	0.1240		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.30		
95% CI	-0.85,0.15		
p-value	0.1400		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	0.02		
95% CI	-0.35,0.60		
p-value	0.8141		
Change from Baseline at 3 hour			
n	18	19	15
Mean (SD)	0.33 (0.670)	1.31 (1.856)	1.26 (1.929)
Median (Min, Max)	0.15 (-0.6, 1.7)	0.70 (0.0, 7.1)	1.00 (0.0, 7.7)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-0.60		
95% CI	-1.20,-0.20		
p-value	0.0027		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.70		
95% CI	-1.40,-0.10		
p-value	0.0161		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	-0.02		
95% CI	-0.60,1.40		
p-value	0.9883		
[1] Wilcoxon Signed Rank Test. Median difference expressed as first named treatment minus second named treatment.			

Table 4: Summary of Area under the Stimulus-Response Curve to Repeated Electrical Muscle Stimulation (cm*mA)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	19	19	18
Mean (SD)	2.78 (1.270)	2.42 (1.331)	2.43 (1.271)
Median (Min, Max)	2.96 (0.2, 4.2)	2.33 (0.1, 4.8)	2.64 (0.1, 4.1)
Change from baseline at 1 hour			
n	18	19	17
Mean (SD)	-0.23 (0.667)	-0.18 (1.158)	0.04 (1.042)
Median (Min, Max)	-0.16 (-2.0, 1.1)	0.02 (-3.0, 1.4)	-0.04 (-1.5, 3.1)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-0.14		
95% CI	-0.72,0.73		
p-value	0.7660		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.16		
95% CI	-0.69,0.50		
p-value	0.5245		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	0.01		
95% CI	-1.14,0.25		
p-value	0.9399		
Change from baseline at 2 hour			
n	18	19	16
Mean (SD)	-0.50 (0.912)	-0.18 (1.207)	-0.67 (1.152)
Median (Min, Max)	-0.48 (-2.3, 1.4)	-0.11 (-3.0, 1.9)	-0.72 (-2.7, 1.3)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-0.35		
95% CI	-0.87,0.37		
p-value	0.2462		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	0.07		
95% CI	-0.50,0.74		
p-value	0.9341		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	0.33		
95% CI	-0.19,1.05		
p-value	0.2979		
Change from baseline at 3 hour			
n	18	19	15
Mean (SD)	-0.44 (1.197)	-0.70 (1.280)	-0.66 (1.279)
Median (Min, Max)	-0.12 (-2.7, 2.3)	-0.03 (-3.4, 0.9)	-0.47 (-2.8, 1.6)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	0.06		
95% CI	-0.37,0.52		
p-value	0.7987		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	0.09		
95% CI	-0.28,0.91		
p-value	0.8552		

Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	-0.15		
95% CI	-0.80,0.46		
p-value	0.5016		
[1] Wilcoxon Signed Rank Test. Median difference expressed as first named treatment minus second named treatment.			
Table 5: Summary of Single Stimulus Pain Detection Threshold to Electrical Skin Stimulation (mA)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	19	19	19
Mean (SD)	6.34 (2.157)	5.78 (1.784)	6.41 (1.957)
Median (Min, Max)	6.50 (3.2, 11.2)	5.30 (3.5, 9.8)	6.20 (2.7, 9.5)
Change from Baseline at 1 hour			
n	19	19	19
Mean (SD)	-0.32 (0.740)	-0.20 (0.832)	-0.42 (1.199)
Median (Min, Max)	-0.20 (-2.0, 0.8)	0.00 (-1.8, 1.5)	-0.20 (-2.9, 1.5)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-0.10		
95% CI	-0.60,0.40		
p-value	0.6783		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	0.10		
95% CI	-0.45,0.75		
p-value	0.6590		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	0.35		
95% CI	-0.50,1.00		
p-value	0.2999		
Change from Baseline at 2 hour			
n	19	19	18
Mean (SD)	0.04 (1.161)	-0.05 (0.859)	-0.32 (1.071)
Median (Min, Max)	-0.20 (-1.5, 3.2)	-0.20 (-1.8, 1.5)	-0.10 (-2.5, 1.7)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	0.05		
95% CI	-0.60,0.75		
p-value	0.8364		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	0.25		
95% CI	-0.40,0.85		
p-value	0.4801		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	0.35		
95% CI	-0.40,1.10		
p-value	0.3519		
Change from Baseline at 3 hour			
n	19	19	18
Mean (SD)	0.27 (1.461)	0.22 (0.747)	-0.12 (1.174)
Median (Min, Max)	0.20 (-2.0, 4.2)	0.30 (-1.0, 1.8)	-0.35 (-2.7, 2.0)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	0.10		
95% CI	-0.80,0.85		
p-value	0.9296		

Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	0.15		
95% CI	-0.45,0.70		
p-value	0.5586		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	0.25		
95% CI	-0.50,1.25		
p-value	0.4375		
[1] Wilcoxon Signed Rank Test. Median difference expressed as first named treatment minus second named treatment.			
Table 6: Summary of Single Stimulus Pain Detection Threshold to Electrical Muscle Stimulation (mA)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	19	19	19
Mean (SD)	2.55 (2.774)	2.38 (1.940)	2.76 (3.244)
Median (Min, Max)	1.60 (0.5, 12.7)	2.00 (0.5, 6.7)	1.70 (0.5, 12.2)
Change from Baseline at 1 hour			
n	18	19	18
Mean (SD)	-0.30 (0.888)	0.57 (2.283)	-0.02 (0.806)
Median (Min, Max.	-0.10 (-3.4, 0.5)	0.10 (-0.8, 9.7)	0.00 (-1.5, 1.5)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-0.35		
95% CI	-0.85,-0.05		
p-value	0.0144		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.20		
95% CI	-0.65,0.25		
p-value	0.3822		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	0.20		
95% CI	-0.20,0.75		
p-value	0.3035		
Change from Baseline at 2 hour			
n	18	19	17
Mean (SD)	-0.01 (1.254)	0.53 (1.620)	0.34 (1.847)
Median (Min, Max)	0.10 (-3.9, 2.5)	0.00 (-0.7, 6.9)	0.00 (-2.3, 6.5)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-0.10		
95% CI	-0.70,0.30		
p-value	0.4796		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.03		
95% CI	-0.80,0.50		
p-value	0.7351		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	0.15		
95% CI	-0.30,1.20		
p-value	0.6956		
Change from Baseline at 3 hour			
n	18	19	17
Mean (SD)	0.07 (1.046)	0.95 (1.867)	0.57 (2.444)
Median (Min, Max)	0.00 (-2.5, 2.2)	0.30 (-0.7, 7.4)	0.10 (-2.2, 9.0)
Treatment comparison			



Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-0.55		
95% CI	-1.45,-0.05		
p-value	0.0276		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.15		
95% CI	-0.90,0.55		
p-value	0.5520		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	0.25		
95% CI	-0.35,1.50		
p-value	0.4254		
[1] Wilcoxon Signed Rank Test. Median difference expressed as first named treatment minus second named treatment.			
Table 7: Summary of Area Under the Stimulus-Response Curve to Single Electrical Skin Stimulation (cm*mA)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	19	19	19
Mean (SD)	2.48 (1.224)	2.50 (1.324)	2.47 (1.315)
Median (Min, Max)	2.58 (0.2, 4.6)	2.54 (0.2, 5.5)	2.52 (0.2, 4.6)
Change from Baseline at 1 hour			
n	19	19	19
Mean (SD)	-0.06 (0.594)	0.03 (0.654)	0.05 (0.359)
Median (Min, Max)	-0.07 (-1.5, 1.1)	0.09 (-2.1, 1.0)	0.08 (-0.9, 0.5)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-0.12		
95% CI	-0.38,0.23		
p-value	0.3736		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.08		
95% CI	-0.33,0.12		
p-value	0.4109		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	0.06		
95% CI	-0.20,0.30		
p-value	0.4683		
Change from Baseline at 2 hour			
n	19	19	18
Mean (SD)	-0.16 (0.654)	-0.23 (0.774)	0.06 (0.568)
Median (Min, Max)	-0.07 (-1.2, 1.3)	-0.08 (-2.6, 0.8)	0.11 (-1.6, 1.0)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-0.01		
95% CI	-0.46,0.50		
p-value	0.9530		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.16		
95% CI	-0.56,0.25		
p-value	0.4423		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	-0.14		
95% CI	-0.51,0.04		
p-value	0.1212		
Change from Baseline at 3 hour			

n	19	19	18
Mean (SD)	-0.30 (0.719)	-0.13 (0.825)	0.06 (0.570)
Median (Min, Max)	-0.15 (-1.7, 1.2)	0.01 (-2.6, 1.2)	0.31 (-1.2, 0.8)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-0.23		
95% CI	-0.58,0.20		
p-value	0.2413		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.34		
95% CI	-0.71,0.10		
p-value	0.0737		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	-0.05		
95% CI	-0.55,0.30		
p-value	0.8986		
[1] Wilcoxon Signed Rank Test. Median difference expressed as first named treatment minus second named treatment.			
Table 8: Summary of Area Under the Stimulus-Response Curve to Single Electrical Muscle Stimulation (cm*mA)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	19	19	19
Mean (SD)	2.48 (1.412)	2.45 (1.306)	2.52 (1.425)
Median (Min, Max)	2.43 (0.2, 4.7)	2.13 (0.2, 4.9)	2.37 (0.2, 5.1)
Change from Baseline at 1 hour			
n	18	19	18
Mean (SD)	0.05 (0.763)	-0.25 (0.825)	-0.17 (1.024)
Median (Min, Max)	0.12 (-1.8, 1.2)	-0.05 (-2.7, 0.7)	-0.20 (-2.6, 1.7)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	0.19		
95% CI	-0.22,0.81		
p-value	0.3465		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.10		
95% CI	-0.44,0.44		
p-value	0.6055		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	-0.16		
95% CI	-0.69,0.28		
p-value	0.4038		
Change from Baseline at 2 hour			
n	18	19	17
Mean (SD)	-0.28 (1.129)	-0.53 (0.924)	-0.30 (1.104)
Median (Min, Max)	0.04 (-3.5, 1.1)	-0.24 (-2.7, 0.5)	0.12 (-2.3, 1.7)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	0.16		
95% CI	-0.29,0.67		
p-value	0.4951		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-0.24		
95% CI	-0.97,0.38		
p-value	0.4637		

<b>Paracetamol vs. Placebo</b>			
Median Difference <sup>[1]</sup>	-0.35		
95% CI	-0.86,0.21		
p-value	0.2633		
<b>Change from Baseline at 3 hour</b>			
n	18	19	17
Mean (SD)	-0.15 (1.034)	-0.75 (1.060)	-0.27 (1.791)
Median (Min, Max)	-0.04 (-2.7, 1.1)	-0.50 (-2.9, 0.8)	-0.31 (-2.7, 5.3)
<b>Treatment comparison</b>			
<b>Paracetamol + Dextromethorphan vs. Paracetamol</b>			
Median Difference <sup>[1]</sup>	0.54		
95% CI	0.12,1.00		
p-value	0.0101		
<b>Paracetamol + Dextromethorphan vs. Placebo</b>			
Median Difference <sup>[1]</sup>	0.20		
95% CI	-0.54,0.80		
p-value	0.4954		
<b>Paracetamol vs. Placebo</b>			
Median Difference <sup>[1]</sup>	-0.32		
95% CI	-0.93,0.24		
p-value	0.2842		
<i>[1] Wilcoxon Signed Rank Test. Median difference expressed as first named treatment minus second named treatment.</i>			
<b>Table 9: Summary of Responses to a 10 Second 20Hz Electrical Stimulation to Skin And Muscle</b>			
<b>Skin Stimulation- AUC<sup>[1]</sup> (0-10 secs, )</b>			
<b>Treatments</b>	<b>Paracetamol + Dextromethorphan</b>	<b>Paracetamol</b>	<b>Placebo</b>
<b>At Baseline</b>			
n	19	19	19
Mean (SD)	18.72 (13.831)	20.52 (15.184)	18.33(15.096)
Median (Min, Max)	18.10 (0.0, 54.6)	22.20 (0.0, 60.4)	14.70 (0.0, 56.6)
<b>Change from Baseline at 1 hour</b>			
n	19	19	19
Mean (SD)	0.37 (5.274)	-2.13 (5.928)	-0.23 (6.977)
Median (Min, Max)	0.40 (-7.8, 12.8)	-0.50 (-17.7, 5.0)	0.00 (-18.2, 13.4)
<b>Treatment comparison</b>			
<b>Paracetamol + Dextromethorphan vs. Paracetamol</b>			
Median Difference <sup>[2]</sup>	1.75		
95% CI	-2.40,6.80		
p-value	0.4180		
<b>Paracetamol + Dextromethorphan vs. Placebo</b>			
Median Difference <sup>[2]</sup>	-0.90		
95% CI	-3.50,1.85		
p-value	0.5019		
<b>Paracetamol vs. Placebo</b>			
Median Difference <sup>[2]</sup>	-1.30		
95% CI	-5.70,1.05		
p-value	0.2069		
<b>Change from Baseline at 2 hour</b>			
n	19	19	18
Mean (SD)	-1.36 (7.336)	-3.39 (6.304)	-0.86 (5.920)
Median (Min, Max)	0.00 (-17.3, 12.4)	-1.30 (-16.9, 6.7)	-0.30 (-13.2, 12.4)
<b>Treatment comparison</b>			
<b>Paracetamol + Dextromethorphan vs. Paracetamol</b>			
Median Difference <sup>[2]</sup>	1.02		
95% CI	-2.00,5.90		

p-value	0.3750		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	-0.20		
95% CI	-4.90,3.80		
p-value	0.8626		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	-1.30		
95% CI	-5.05,2.10		
p-value	0.3529		
Change from Baseline at 3 hour			
n	19	19	18
Mean (SD)	-1.16 (7.461)	-2.09 (7.628)	-0.58 (7.435)
Median (Min, Max)	0.00 (-16.7, 14.7)	-1.30 (-19.3, 10.9)	-0.45 (-13.9, 15.8)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	1.07		
95% CI	-4.35,4.85		
p-value	0.7099		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	-0.30		
95% CI	-5.40,3.80		
p-value	0.8445		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	-1.00		
95% CI	-5.80,5.40		
p-value	0.6198		
Skin Stimulation- AUC <sup>[1]</sup> (10-15 secs)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	19	19	19
Mean (SD)	0.33 (0.817)	0.65 (2.325)	0.01 (0.046)
Median (Min, Max)	0.00 (0.0, 2.8)	0.00 (0.0, 10.0)	0.00 (0.0, 0.2)
Change from Baseline at 1 hour			
n	19	19	19
Mean (SD)	-0.32 (0.820)	-0.59 (2.139)	0.14 (0.434)
Median (Min, Max)	0.00 (-2.8, 0.0)	0.00 (-9.2, 0.0)	0.00 (0.0, 1.6)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-0.10,0.00		
p-value	1.0000		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-0.30,0.00		
p-value	0.2500		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-0.80,0.00		
p-value	0.1250		
Change from Baseline at 2 hour			
n	19	19	18
Mean (SD)	-0.32 (0.820)	-0.63 (2.309)	0.06 (0.289)
Median (Min, Max)	0.00 (-2.8, 0.0)	0.00 (-9.9, 0.3)	0.00 (-0.2, 1.2)
Treatment comparison			

Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-0.25,0.00		
p-value	1.0000		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-0.30,0.00		
p-value	0.1250		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-0.45,0.00		
p-value	0.2500		
Change from Baseline at 3 hour			
n	19	19	18
Mean (SD)	-0.28 (0.846)	-0.55 (1.920)	0.01 (0.087)
Median (Min, Max)	0.00 (-2.8, 0.6)	0.00 (-8.2, 0.0)	0.00 (-0.2, 0.3)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-0.10,0.30		
p-value	0.9375		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-0.15,0.00		
p-value	0.3438		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	0.00		
95% CI	0.00,0.00		
p-value	0.5000		
Skin Stimulation- Time to Peak Visual Analogue Scale (VAS) (sec)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	18	18	18
Mean (SD)	7.24 (1.766)	6.79 (2.149)	6.76 (2.133)
Median (Min, Max)	8.20 (3.6, 8.8)	8.00 (2.2, 8.8)	8.00 (2.8, 9.0)
At 1 hour			
n	18	18	15
Mean (SD)	6.63 (1.829)	7.24 (1.427)	6.99 (1.647)
Median (Min, Max)	7.40 (3.0, 8.4)	7.40 (3.0, 9.0)	7.80 (4.6, 9.0)
At 2 hour			
n	18	16	16
Mean (SD)	5.98 (2.028)	6.41 (2.128)	6.51 (2.007)
Median (Min, Max)	6.80 (2.2, 8.4)	7.00 (2.6, 9.0)	6.90 (3.2, 9.0)
At 3 hour			
n	18	17	16
Mean (SD)	6.18 (1.891)	6.32 (2.210)	7.01 (1.812)
Median (Min, Max)	7.00 (2.4, 8.6)	6.80 (2.4, 9.2)	8.00 (3.6, 8.8)
Muscle Stimulation- AUC <sup>[1]</sup> (0-10 secs)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	18	18	18
Mean (SD)	22.47 (15.024)	21.23 (17.824)	20.25 (18.772)
Median (Min, Max)	20.10 (0.4, 48.1)	18.25 (0.0, 62.5)	16.45 (0.0, 71.9)

Change from Baseline at 1 hour			
n	18	18	17
Mean (SD)	-0.99 (9.119)	-5.34 (8.278)	-2.31 (12.949)
Median (Min, Max)	-2.60 (-21.5, 19.3)	-1.75 (-19.4, 4.3)	-0.50 (-34.7, 14.9)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	4.90		
95% CI	-1.50,11.20		
p-value	0.1232		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	-1.78		
95% CI	-8.15,5.20		
p-value	0.5995		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	-3.70		
95% CI	-13.25,0.50		
p-value	0.0748		
Change from Baseline at 2 hour			
n	18	18	15
Mean (SD)	-4.17 (13.736)	-7.01 (9.660)	-6.13 (17.483)
Median (Min, Max)	-1.10 (-32.5, 21.9)	-4.40 (-26.2, 4.8)	0.00 (-60.3, 8.7)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	1.90		
95% CI	-2.30,8.00		
p-value	0.3529		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	-0.35		
95% CI	-9.90,14.65		
p-value	1.0000		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	-1.00		
95% CI	-10.95,8.25		
p-value	0.8552		
Change from Baseline at 3 hour			
n	17	18	15
Mean (SD)	-2.15 (14.141)	-9.12 (10.791)	-8.77 (20.558)
Median (Min, Max)	0.40 (-29.2, 21.9)	-2.85 (-29.0, 1.5)	-4.70 (-70.8, 11.8)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	7.60		
95% CI	-0.15,14.85		
p-value	0.0507		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	0.75		
95% CI	-6.60,15.55		
p-value	0.8552		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	-2.15		
95% CI	-14.90,9.50		
p-value	0.5016		
Muscle Stimulation- AUC <sup>[1]</sup> (10-15 secs)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			

n	18	18	18
Mean (SD)	0.87 (3.211)	0.39 (0.941)	0.17 (0.513)
Median (Min., Max.)	0.00 (0.0, 13.7)	0.00 (0.0, 3.4)	0.00 (0.0, 2.0)
Change from Baseline at 1 hour			
n	18	18	17
Mean (SD)	0.27 (1.238)	-0.08 (0.753)	0.01 (0.744)
Median (Min, Max)	0.00 (-1.1, 5.0)	0.00 (-2.0, 2.0)	0.00 (-2.0, 2.2)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	0.15		
95% CI	0.00,0.80		
p-value	0.1602		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	0.00		
95% CI	0.00,1.40		
p-value	0.4688		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-0.65,0.00		
p-value	0.4375		
Change from Baseline at 2 hour			
n	18	18	15
Mean (SD)	-0.48 (3.381)	-0.04 (0.537)	0.37 (1.680)
Median (Min, Max)	0.00 (-13.7, 2.3)	0.00 (-2.0, 0.8)	0.00 (-2.0, 6.0)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-0.15,1.00		
p-value	0.4414		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-0.20,0.25		
p-value	0.8125		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-1.15,0.25		
p-value	0.5625		
Change from Baseline at 3 hour			
n	17	18	15
Mean (SD)	0.76 (2.369)	0.01 (1.943)	0.41 (2.442)
Median (Min, Max)	0.00 (-0.3, 9.7)	0.00 (-3.2, 6.9)	0.00 (-2.0, 9.0)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	0.25		
95% CI	0.00,2.00		
p-value	0.0313		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-0.15,0.95		
p-value	0.5625		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	-0.10		
95% CI	-1.20,0.00		
p-value	0.1563		

Muscle Stimulation- Time to Peak Visual Analogue Scale (VAS) (sec)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	18	15	15
Mean (SD)	7.32 (1.816)	6.63 (2.089)	7.29 (1.756)
Median (Min, Max)	8.10 (3.0, 9.8)	6.60 (3.0, 9.8)	8.00 (2.8, 9.2)
At 1 hour			
n	17	15	16
Mean (SD)	7.14 (1.998)	6.27 (2.465)	5.86 (1.715)
Median (Min, Max)	7.80 (3.8, 10.0)	7.60 (2.4, 9.4)	5.70 (3.2, 9.0)
At 2 hour			
n	17	15	12
Mean (SD)	7.18 (1.675)	6.00 (2.505)	6.98 (2.208)
Median (Min, Max)	7.80 (4.4, 10.0)	5.80 (1.8, 9.6)	7.80 (2.4, 9.0)
At 3 hour			
n	16	13	13
Mean (SD)	6.05 (2.528)	6.06 (2.416)	6.02 (2.225)
Median (Min, Max)	6.30 (1.2, 9.8)	6.40 (2.4, 9.0)	6.60 (1.6, 9.0)
Level of pain is measured continuously over a 15 second period on a 10cm VAS where 0 = No pain and 10 = Worst imaginable pain.			
[1] AUC = Area under the VAS-time curve (cm*sec).			
[2] Wilcoxon Signed Rank Test. Median difference expressed as first named treatment minus second named treatment.			
Table 10: Summary Of Responses To A 10 Second 2 Hz Electrical Stimulation To Skin And Muscle			
Skin Stimulation- AUC <sup>[1]</sup> (0-10 secs)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	19	19	19
Mean (SD)	13.51 (13.374)	14.07 (13.373)	11.13 (14.352)
Median (Min, Max)	12.70 (0.0, 50.6)	10.10 (0.0, 48.6)	8.40 (0.0, 64.6)
Change from Baseline at 1 hour			
n	19	19	19
Mean (SD)	-2.94 (7.660)	-1.92 (8.343)	0.31 (6.575)
Median (Min, Max)	-0.30 (-25.8, 13.1)	-0.20 (-20.8, 15.3)	0.00 (-14.0, 14.4)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	0.95		
95% CI	-5.50,5.00		
p-value	0.5614		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	-2.95		
95% CI	-5.90,0.00		
p-value	0.0302		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	-2.80		
95% CI	-6.50,1.05		
p-value	0.1354		
Change from Baseline at 2 hour			
n	19	19	18
Mean (SD)	-5.86 (7.784)	-0.87 (6.725)	-0.97 (8.452)
Median (Min, Max)	-0.80 (-20.0, 5.3)	0.00 (-17.4, 9.6)	-0.55 (-23.7, 22.7)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	-2.83		
95% CI	-9.35,0.00		
p-value	0.0302		



Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	-2.45		
95% CI	-7.35,0.50		
p-value	0.1070		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	0.05		
95% CI	-2.95,5.85		
p-value	0.9780		
Change from Baseline at 3 hour			
n	19	19	18
Mean (SD)	-4.56 (9.717)	-2.79 (7.899)	-2.08 (7.793)
Median (Min, Max)	-1.70 (-21.9, 16.9)	0.00 (-25.1, 11.6)	-0.30 (-28.4, 8.5)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	-0.38		
95% CI	-7.95,4.00		
p-value	0.7157		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	-1.65		
95% CI	-7.25,1.80		
p-value	0.2744		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	-0.70		
95% CI	-5.40,3.55		
p-value	0.6387		
Skin Stimulation- AUC <sup>[1]</sup> (10-15 secs)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	19	19	19
Mean (SD)	0.63 (1.111)	0.69 (1.069)	0.65 (0.688)
Median (Min, Max)	0.30 (0.0, 3.7)	0.20 (0.0, 3.6)	0.50 (0.0, 2.1)
Change from Baseline at 1 hour			
n	19	19	19
Mean (SD)	-0.06 (0.687)	-0.22 (0.554)	-0.22 (0.601)
Median (Min, Max)	0.00 (-2.2, 0.7)	-0.10 (-2.0, 0.8)	0.00 (-1.5, 0.8)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	0.10		
95% CI	-0.05,0.50		
p-value	0.2236		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	0.20		
95% CI	-0.20,0.55		
p-value	0.2368		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	-0.05		
95% CI	-0.40,0.30		
p-value	0.6697		
Change from Baseline at 2 hour			
n	19	19	18
Mean (SD)	-0.29 (0.665)	-0.33 (0.571)	-0.26 (0.628)
Median (Min, Max)	0.00 (-2.4, 0.3)	-0.10 (-2.0, 0.3)	-0.05 (-1.8, 0.8)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			

Median Difference <sup>[2]</sup>	0.05		
95% CI	-0.15,0.30		
p-value	0.5081		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-0.25,0.40		
p-value	0.8921		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	0.00		
95% CI	-0.15,0.20		
p-value	0.9648		
Change from Baseline at 3 hour			
n	19	19	18
Mean (SD)	0.05 (1.583)	-0.39 (0.642)	-0.40 (0.582)
Median (Min, Max)	0.00 (-2.6, 6.0)	-0.10 (-2.3, 0.1)	-0.20 (-1.8, 0.5)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	0.20		
95% CI	-0.05,0.60		
p-value	0.0801		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	0.35		
95% CI	-0.05,0.70		
p-value	0.0785		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	-0.05		
95% CI	-0.40,0.35		
p-value	0.8555		
Skin Stimulation- Time to Peak Visual Analogue Scale (VAS) (sec)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	14	15	16
Mean (SD)	8.10 (1.899)	7.91 (2.454)	6.91 (2.665)
Median (Min, Max)	8.60 (4.2, 10.0)	9.20 (2.0, 10.0)	7.40 (2.0, 10.0)
At 1 hour			
n	15	15	14
Mean (SD)	7.00 (2.972)	6.69 (2.660)	6.93 (3.235)
Median (Min, Max)	8.80 (2.6, 10.0)	6.80 (2.2, 9.8)	8.00 (0.0, 10.0)
At 2 hour			
N	14	15	13
Mean (SD)	6.77 (2.677)	6.69 (2.706)	7.89 (2.029)
Median (Min, Max)	7.50 (2.0, 10.0)	6.60 (1.6, 9.8)	8.60 (3.6, 9.8)
At 3 hour			
N	15	15	13
Mean (SD)	6.91 (3.037)	6.23 (3.004)	7.17 (2.918)
Median (Min, Max)	7.80 (2.2, 10.0)	6.80 (2.4, 10.0)	8.80 (2.4, 10.0)
Muscle Stimulation- AUC <sup>[1]</sup> (0-10 secs)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	18	19	18
Mean (SD)	15.50 (13.315)	16.87 (16.539)	17.63 (16.144)
Median (Min, Max)	13.15 (0.0, 43.8)	15.40 (0.0, 69.5)	16.00 (0.0, 66.3)
Change from Baseline at 1 hour			

n	18	19	17
Mean (SD)	-0.35 (12.424)	-4.49 (9.004)	-5.19 (11.388)
Median (Min, Max)	-0.75 (-33.1, 23.3)	-2.80 (-26.8, 10.9)	-2.70 (-37.5, 11.0)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	4.20		
95% CI	-4.15,11.65		
p-value	0.2522		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	0.40		
95% CI	-8.05,11.25		
p-value	0.8674		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	-1.23		
95% CI	-5.60,5.20		
p-value	0.6092		
Change from Baseline at 2 hour			
n	17	19	16
Mean (SD)	-4.37 (12.366)	-7.12 (13.262)	-9.76 (15.432)
Median (Min, Max)	-0.40 (-30.5, 16.0)	-2.80 (-40.3, 14.0)	-6.40 (-60.1, 5.5)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	1.15		
95% CI	-5.20,10.35		
p-value	0.7436		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	3.05		
95% CI	-5.90,15.65		
p-value	0.4263		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	1.93		
95% CI	-3.90,8.30		
p-value	0.5282		
Change from Baseline at 3 hour			
n	18	19	15
Mean (SD)	-3.81 (13.274)	-6.63 (10.856)	-12.66 (18.708)
Median (Min, Max)	-2.05 (-33.8, 21.9)	-3.10 (-32.7, 7.5)	-10.80 (-66.2, 6.8)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	0.90		
95% CI	-3.50,6.90		
p-value	0.6863		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	6.65		
95% CI	-3.85,18.55		
p-value	0.2478		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	2.70		
95% CI	-5.25,16.40		
p-value	0.5416		
Muscle Stimulation- AUC <sup>[1]</sup> (10-15 secs)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	18	19	18

Mean (SD)	1.06 (1.835)	1.37 (2.204)	1.56 (2.179)
Median (Min, Max)	0.25 (0.0, 7.4)	0.70 (0.0, 9.1)	0.35 (0.0, 7.0)
Change from Baseline at 1 hour			
n	18	19	17
Mean (SD)	-0.14 (0.835)	-0.56 (1.259)	-0.51 (1.513)
Median (Min, Max)	0.00 (-2.1,1.6)	-0.30 (-4.2, 1.6)	0.00 (-3.6, 2.4)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	0.20		
95% CI	-0.15,1.15		
p-value	0.2799		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	0.13		
95% CI	-0.55,1.00		
p-value	0.6848		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	-0.25		
95% CI	-1.10,0.45		
p-value	0.3022		
Change from Baseline at 2 hour			
n	17	19	16
Mean (SD)	-0.51 (0.956)	-0.68 (1.284)	-0.82 (1.429)
Median (Min, Max)	0.00 (-2.7, 0.2)	-0.30 (-4.2, 0.8)	-0.15 (-4.5, 0.9)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	0.10		
95% CI	-0.35,0.55		
p-value	0.6588		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	0.12		
95% CI	-0.45,0.75		
p-value	0.8286		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	0.10		
95% CI	-0.60,0.70		
p-value	0.7081		
Change from Baseline at 3 hour			
n	18	19	15
Mean (SD)	0.78 (5.111)	-0.84 (1.852)	-1.19 (2.150)
Median (Min, Max)	0.00 (-2.8, 20.8)	-0.50 (-6.2, 1.9)	-0.10 (-7.0, 0.8)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	0.35		
95% CI	-0.30,0.90		
p-value	0.2481		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	0.40		
95% CI	-0.45,1.10		
p-value	0.2651		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	0.10		
95% CI	-0.65,1.20		
p-value	0.6233		
Muscle Stimulation- Time to Peak Visual Analogue Scale VAS (sec)			

Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	15	17	16
Mean (SD)	8.07 (2.641)	7.92 (2.729)	7.56 (2.224)
Median (Min, Max)	9.60 (2.4, 10.0)	8.80 (1.4, 10.0)	7.70 (3.4, 10.0)
At 1 hour			
n	15	13	15
Mean (SD)	6.61 (2.244)	7.89 (2.147)	7.36 (2.137)
Median (Min, Max)	7.00 (2.4, 10.0)	8.80 (4.0, 10.0)	7.20 (3.0, 10.0)
At 2 hour			
n	14	15	12
Mean (SD)	6.10 (2.212)	6.56 (2.351)	6.87 (2.917)
Median (Min, Max)	5.80 (2.4, 9.6)	6.40 (2.4, 9.8)	6.30 (2.4, 10.0)
At 3 hour			
n	15	12	11
Mean (SD)	6.89 (3.002)	6.55 (2.351)	7.29 (2.502)
Median (Min, Max)	8.00 (2.2, 10.0)	6.80 (1.4, 9.8)	8.00 (3.4, 10.2)
Level of pain is measured continuously over a 15 second period on a 10cm VAS where 0 = No pain and 10 = Worst imaginable pain.			
[1] AUC = Area under the VAS-time curve (cm*sec).			
[2] Wilcoxon Signed Rank Test. Median difference expressed as first named treatment minus second named treatment.			
Table 11: Summary of Responses to Pressure Pain Threshold (PPT, kPa)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	19	19	19
Mean (SD)	413.8 (191.13)	414.1 (118.57)	430.3 (165.67)
Median (Min, Max)	358.0 (165, 863)	442.0 (188, 627)	409.0 (163, 766)
Change from Baseline at 1 hour			
n	19	19	19
Mean (SD)	0.7 (138.29)	-28.7 (88.30)	-8.2 (98.31)
Median (Min, Max)	-3.0 (-354, 379)	13.0 (-256, 46)	11.0 (-214, 130)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	25.00		
95% CI	-44.00,99.00		
p-value	0.3791		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	17.50		
95% CI	-63.50,109.50		
p-value	0.4616		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	-20.00		
95% CI	-64.00,23.50		
p-value	0.3465		
Change from Baseline at 2 hour			
n	19	19	18
Mean (SD)	-13.4 (138.50)	-19.4 (75.38)	6.8 (91.12)
Median (Min, Max)	-18.0 (-406, 267)	3.0 (-232, 92)	6.5 (-158, 225)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	20.50		
95% CI	-50.50,84.00		
p-value	0.6156		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-15.50		

95% CI	-81.00,61.50		
p-value	0.5509		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	-26.00		
95% CI	-65.50,15.50		
p-value	0.2484		
Change from Baseline at 3 hour			
n	19	19	18
Mean (SD)	-16.1 (171.31)	-42.4 (98.94)	-7.3 (104.33)
Median (Min, Max)	-14.0 (-355, 360)	-20.0 (-252, 148)	7.5 (-205, 178)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	28.00		
95% CI	-78.00,127.00		
p-value	0.5610		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	12.50		
95% CI	-54.50,80.00		
p-value	0.6095		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	-34.00		
95% CI	-89.00,23.00		
p-value	0.2462		
[1] Wilcoxon Signed Rank Test. Median difference expressed as first named treatment minus second named treatment.			
Table 12: Summary Of Responses To Pressure Pain Tolerance Threshold (kPa)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	19	19	19
Mean (SD)	815.9 (424.72)	698.8 (274.58)	804.2 (377.05)
Median (Min, Max)	668.0 (318, 1939)	638.0 (295, 1442)	644.0 (380, 1652)
Change from Baseline at 1 hour			
n	19	19	19
Mean (SD)	-69.7 (191.24)	31.8 (197.62)	-22.5 (208.05)
Median (Min, Max)	-35.0 (-517, 209)	14.0 (-253, 627)	-54.0 (-457, 296)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-69.75		
95% CI	-228.5,48.00		
p-value	0.2753		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-30.50		
95% CI	-159.0,131.50		
p-value	0.7337		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	56.00		
95% CI	-85.00,191.50		
p-value	0.3927		
Change from Baseline at 2 hour			
n	19	19	18
Mean (SD)	-96.2 (182.65)	-54.3 (150.31)	-31.4 (207.52)
Median (Min, Max)	-63.0 (-626, 301)	-61.0 (-314, 199)	0.5 (-504, 329)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-51.00		

95% CI	-186.0,104.50		
p-value	0.5153		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	-41.00		
95% CI	-177.5,100.00		
p-value	0.5724		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	-30.50		
95% CI	-125.5,62.50		
p-value	0.5226		
Change from Baseline at 3 hour			
n	19	19	18
Mean (SD)	-62.9 (337.35)	58.3 (186.58)	-108.2 (185.67)
Median (Min, Max)	-5.0 (-1241, 478)	18.0 (-288, 383)	-89.5 (-50, 217)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[1]</sup>	-83.75		
95% CI	-254.5,86.00		
p-value	0.1564		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[1]</sup>	125.50		
95% CI	-27.50,249.00		
p-value	0.0665		
Paracetamol vs. Placebo			
Median Difference <sup>[1]</sup>	154.50		
95% CI	16.00,302.00		
p-value	0.0294		
[1] Wilcoxon Signed Rank Test. Median difference expressed as first named treatment minus second named treatment.			
Table 13: Summary Of Responses To Intra-Muscular Injection Of Hypertonic Saline			
AUC (0-7 mins) <sup>[1]</sup>			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	18	18	18
Mean (SD)	493.82 (376.950)	648.50 (393.461)	526.44 (381.992)
Median (Min, Max)	473.70 (0.0, 1056.8)	670.20 (0.0, 1501.9)	485.65 (0.0, 1264.1)
Change from Baseline at 2 hour			
n	18	18	16
Mean (SD)	-23.22 (251.328)	-81.67 (265.481)	-55.34 (342.768)
Median (Min, Max)	-40.65 (-414.5, 500.8)	-99.00 (-507.6, 443.1)	-54.80 (-743.5, 735.1)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	95.40		
95% CI	-60.35,274.20		
p-value	0.1901		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	1.48		
95% CI	-177.5,355.60		
p-value	1.0000		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	-9.00		
95% CI	-181.0,221.20		
p-value	0.9341		
Maximum Pain Intensity (cm)			

Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	18	18	17
Mean (SD)	3.78 (2.707)	4.21 (2.220)	4.33 (2.637)
Median (Min, Max)	3.70 (0.0, 9.5)	4.05 (0.0, 8.4)	5.00 (0.0, 8.4)
Change from Baseline at 2 hour			
n	19	18	15
Mean (SD)	3.54 (3.147)	4.12 (2.788)	3.50 (2.606)
Median (Min, Max)	2.00 (0.0, 9.8)	3.65 (0.0, 8.0)	2.70 (0.0, 8.0)
Time to Max. Pain (min)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	17	17	17
Mean (SD)	1.38 (0.597)	1.87 (0.786)	1.42 (0.670)
Median (Min, Max)	1.60 (0.4, 2.4)	1.80 (0.8, 4.0)	1.60 (0.4, 2.6)
Change from Baseline at 2 hour			
n	17	16	14
Mean (SD)	1.24 (0.702)	1.59 (0.848)	1.46 (0.693)
Median (Min, Max)	1.20 (0.0, 2.9)	1.45 (0.6, 3.8)	1.35 (0.5, 2.9)
Local Pain Area (cm^2)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	19	18	18
Mean (SD)	33.91 (47.118)	43.22 (52.947)	42.01 (58.496)
Median (Min, Max)	7.10 (0.0, 174.4)	15.25 (0.0, 161.4)	17.25 (0.0, 205.3)
Change from Baseline at 2 hour			
n	19	18	17
Mean (SD)	-2.12 (15.451)	-4.55 (30.960)	-9.99 (20.506)
Median (Min, Max)	-0.20 (-35.9, 21.9)	0.00 (-79.4, 71.6)	-5.90 (-43.5, 31.6)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	1.10		
95% CI	-14.90,16.95		
p-value	0.8209		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	6.15		
95% CI	-8.75,21.30		
p-value	0.2979		
Paracetamol vs. Placebo			
Median Difference <sup>[3]</sup>	7.55		
95% CI	-3.65,24.45		
p-value	0.2524		
Referred Pain Area developed the pain (cm^2)			
Treatments	Paracetamol + Dextromethorphan	Paracetamol	Placebo
At Baseline			
n	8	10	9
Mean (SD)	21.79 (16.181)	16.08 (10.827)	32.41 (22.469)
Median (Min, Max)	18.45 (3.3, 47.6)	13.65 (2.9, 31.8)	22.70 (4.5, 80.7)
Change from Baseline at 2 hour			
n	8	7	7
Mean (SD)	7.60 (14.508)	12.73 (33.417)	-9.47 (9.933)



Median (Min, Max)	4.70 (-8.2, 30.2)	3.50 (-24.0, 82.1)	-6.30 (-28.2, 0.6)
Treatment comparison			
Paracetamol + Dextromethorphan vs. Paracetamol			
Median Difference <sup>[2]</sup>	4.70		
95% CI	-8.60,26.20		
p-value	0.2188		
Paracetamol + Dextromethorphan vs. Placebo			
Median Difference <sup>[2]</sup>	19.90		
95% CI	-1.90,39.80		
p-value	0.0625		
Paracetamol vs. Placebo			
Median Difference <sup>[2]</sup>	16.00		
95% CI	0.40,98.60		
p-value	0.0313		
N= number of subjects analysed for respective outcome measure. Level of pain is measured continuously over a 7 minute period on a 10cm VAS where 0 = No pain and 10 = Worst imaginable pain. [1] AUC = Area under the VAS-time curve 0 to 7 mins (cm*sec). [2] Wilcoxon Signed Rank Test. Median difference expressed as first named treatment minus second named treatment.			
Safety Results (Safety population, N=20):			
Table 14: Treatment Emergent Adverse Events(AEs)			
Treatments	Paracetamol + Dextromethorphan N=20	Paracetamol N=20	Placebo N=20
Number Of Subjects With at Least One AE, n (%)	3 (15.0)	0	1 (5.0)
System Organ Class/ Preferred Term			
Infections And Infestations			
Influenza	2 (10.0)	0	0
Musculoskeletal And Connective Tissue Disorders			
Muscle Spasms	1 (5.0)	0	0
Skin And Subcutaneous Tissue Disorders			
Urticaria	0	0	1 (5.0)
Serious Adverse Events (SAEs) - On-Therapy			
No SAE was reported.			