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

Study Number: A3360529

Title: A Randomised, Double-Blind, Evaluation of the Effects of Paracetamol on the Blood Oxygen Level-Dependent (BOLD) functional magnetic resonance imaging (fMRI) Response to Painful Stimuli in Subjects with Osteoarthritis.

Rationale: The objective of this study was to investigate if fMRI can detect the effects of a known pain medicine at over-the- counter doses in people with osteoarthritis (OA) of the knee. The fMRI is a harmless and painless technique that was used in the current study to collect images of brain activity to see if is changed when feeling pain.

Phase: IV

Study Period: 9th September 2010 to 17th August 2011

Study Design: Single-center, placebo-controlled, double blind, 3-way crossover study to evaluate the effect of Paracetamol on the BOLD fMRI response to pressure stimuli in subjects with Osteoarthritis. There were three study sessions: one session following treatment with four consecutive doses of an 8-hour sustained release paracetamol formulation, another session following treatment with four consecutive doses of matched placebo, and another session during which no treatment will be administered. The no treatment arm was scheduled in the first or second study session.

Centres: 1 in Spain

Indication: Analgesia

Treatment:

Test Group: Two 665 mg sustained release paracetamol caplets – 1330 mg paracetamol taken orally with 150 milliliters (ml) of water

Placebo Group: Two caplets of matched placebo taken orally with 150ml of water.

No treatment Group: No treatment at all.

Objectives:

Primary Objective:

To compare the BOLD response to mechanical stimulation via pressure stimuli applied to the tibio-femoral joint in subjects with knee OA following treatment with four consecutive doses of either a test formulation, or four consecutive doses of matched placebo.

Secondary Objectives:

1. To compare the BOLD response to pressure stimuli applied to the tibio-femoral joint in subjects with knee OA between the treatment with four consecutive doses of test formulation and no treatment session, and between placebo and no treatment session.
2. To compare the BOLD response to pressure stimuli applied to the patello-femoral joint in subjects with knee OA between treatment with four consecutive doses of test compared to placebo formulation and no treatment session, and between placebo and no treatment session.
3. To compare the subjective numerical rating scale (NRS) response to pressure applied to the tibio-femoral joint in subjects with knee OA following treatment with four consecutive doses of test formulation and no treatment session, and between placebo and no treatment session.
4. To compare the subjective NRS response to pressure applied to the patella-femoral joint in subjects with knee OA following treatment with four consecutive doses of test formulation and no treatment session, and between placebo and no treatment session

Primary Efficacy Variable:

BOLD responses to painful pressure stimuli applied to the OA knee in the tibio-femoral joint.

Secondary Efficacy Variable(s):

1. BOLD responses to pressure stimuli applied to the OA knee in the patello-femoral joint.
2. Numerical (11-point) pain ratings in response to painful pressure stimuli applied to the OA knee in the tibio-femoral joint.
3. Numerical (11-point) pain ratings in response to painful pressure stimuli applied to the OA knee in the patello-femoral joint

Statistical Methods:

Bold responses (MRI numeric values) for each brain region were analyzed separately, using a paired t-test for mean of differences between any two treatments across subjects that took those two treatments.
NRS endpoints were analyzed using ANCOVA in a Mixed Model, with treatments as a fixed effect and subjects as a random effect. Period and baseline NRS (NRS assessment during pre-screening) were used as covariates. Mean of each treatment was compared against the respective baseline using a t-test (H0: LS Mean = 0) to test if there was a significant effect of treatment as compared to the baseline (pre-treatment). NRS responses (change from baseline) among treatments were also compared using multiple comparisons in ANCOVA. All comparisons were performed at P=0.05, using Proc Mixed of SAS (SAS v. 9.2).

Study Population:

	Overall
Number of Subjects:	
Planned, N	50
Randomized, N	31
Completed, n (%)	27 (87.10)
Total Number Subjects Withdrawn, N (%)	4 (12.90%)
Withdrawn due to Adverse Events, n (%)	3 (9.68)
Withdrawn due to Protocol Deviation, n (%)	1 (3.23)
N (intent to treat [ITT] population)	25
Demographics (Safety Population)	
N (Safety Population)	30
Females: Males	26: 4
Mean Age, years (SD)	68.5 (7.97)
White, n (%)	30 (100.0)

Primary Efficacy Results: Visual inspection showed activation of brain activities by painful stimulation of the tibio-femoral joint in no treatment panels which reflects the “baseline” activation pattern by this painful stimulation (Figure 1) (images from representative patient). Similar activation patterns were observed in the paracetamol treatment panels compared to the no treatment group. In addition, similar, but less extensive activation patterns were observed in the placebo treatment panels (Figure 1). No statistically significant difference of the BOLD signal was found in different brain regions among three treatment groups.

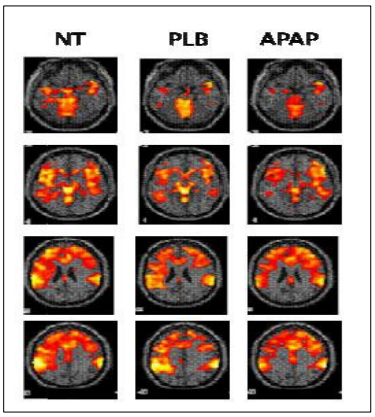
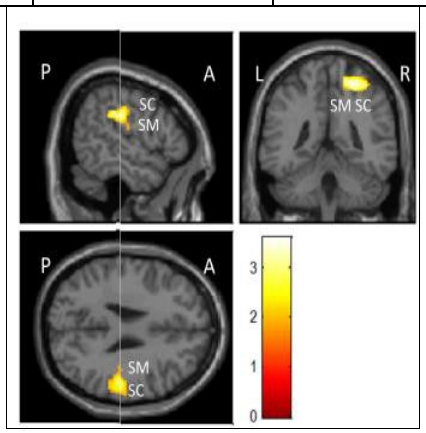


Figure 1: Brain activity patterns for each treatment condition after painful stimulation of the tibio-femoral.
NT: No treatment, PLB: Placebo, APAP: Test Formulation. Images from top to bottom are from progressively superior cross-sections

Secondary Efficacy Results

Table 1: Reduction of brain activation (BOLD) after painful stimulation in patello-femoral joint during treatment with Test formulation as compared to no treatment[1]

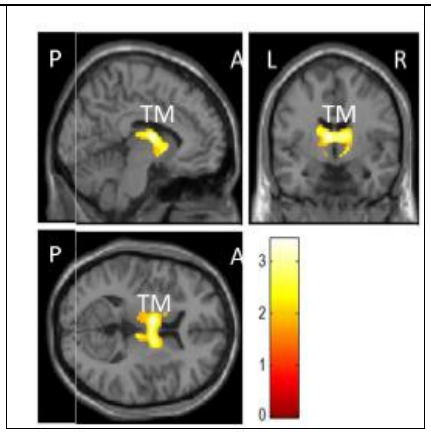
Brain region	Cluster size[2] (num of voxels)	MNI[3] Coordinates	Mean Difference[4]	T[5]	p-value[6] (uncorrected) Voxel level
Sensory cortex (a)	112	24 -44 62	-0.3153	-3.60	0.0022
Supramarginal gyrus	134	56 -32 30	-0.2955	-3.42	0.0033



A: Anterior of Brain; P: Posterior of brain; L: Left side of brain; R: Right side of brain; SC: Sensory Cortex; SM: Supramarginal gyrus

Table 2: Reduction of brain activation (BOLD) after painful stimulus in patello-femoral joint during treatment with placebo as compared to Test formulation[1]

Brain region	Cluster size[2] (num of voxels)	MNI[3] Coordinates	Mean Difference[4]	T[5]	p-value[6] (uncorrected) Voxel level
Thalamus	343	-6 -4 12	-1.1651	-3.44	0.0031

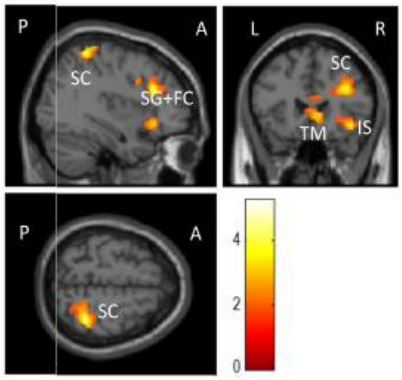


A: Anterior of Brain; P: Posterior of brain; L: Left side of brain; R: Right side of brain; TM: Thalamus

Table 3: Reduction of brain activation (BOLD) after painful stimulation on patello-femoral during treatment with placebo as compared to no treatment[1]

Brain region	Cluster size[2] (num of voxels)	MNI[3] Coordinates	Mean Difference[4]	T[5]	p-value[6] (uncorrected) Voxel level
Subgenu	116	6 28 0	-0.4541	-5.26	<.0001
Frontal cortex	305	38 26 26	-0.3031	-4.10	0.0007
Insula	63	40 26 -10	-0.5008	-3.47	0.0029
Sensory cortex (b)	176	36 -44 62	-0.5502	-4.49	0.0003

1) This table shows only comparisons with a significant difference from a series of multiple comparisons among all the brain regions.
2) Cluster size representing number of gathered voxels forming an anatomical unit whose intensity exceeds a preselected cluster threshold.
3) Maximum peak coordinates for the specific cluster as defined by MNI template (the default space used by SPM program).
4) Mean of difference is calculated as mean of differences of MRI numeric values between placebo and no treatment for each subject.
5) T-test from paired comparison testing: H_0: Mean difference (Placebo – No Treatment) = 0
6) p-value associated with paired T test.



A: Anterior of Brain; P: Posterior of brain; L: Left side of brain; R: Right side of brain; SC: Sensory Cortex; SG: Subgenual prefrontal cortex; FC: Frontal cortex; IS: Insula; TM: Thalamus

Table 4 :Effect of treatment on tibio-femoral stimulation before and after the fMRI scan (NRS Assessment)

Statistics/ Comparisons	PreScan			Post Scan		
	Test Group	Placebo Group	No Treatment Group	Test Group	Placebo Group	No Treatment Group
Mean (SD)[1A]	0.55 (0.89)	0.17 (1.07)	0 (0.74)	0.15 (1.18)	0.09 (1.38)	-0.13 (1.10)
LS Mean 95% CI[2]	0.57 0.12, 1.02	0.23 0.19, 0.66	0.10 -0.36, 0.55	0.06 -0.56, 0.67	0.06 -0.52, 0.65	-0.1 -0.72, 0.53
p-value[3]	0.0139	0.2713	0.6723	0.8561	0.8220	0.7534

Comparison	Difference[4]	95% CI[5]	p-value[6]	Difference[4]	95% CI[5]	p-value[6]
Test vs. Placebo	0.34	-0.12, 0.80	0.1459	-0.01	-0.63, 0.61	0.9749
Test vs. No treatment	0.48	-0.06, 1.01	0.0782	0.15	-0.56, 0.87	0.6679
Placebo vs. No treatment	0.14	-0.38, 0.65	0.5897	0.16	-0.53, 0.85	0.6363

Table 5 :Effect of treatment on patello-femoral stimulation before and after the fMRI scan (NRS Assessment)

Statistics/ Comparisons	PreScan			Post Scan		
	Test Group	Placebo Group	No Treatment Group	Test Group	Placebo Group	No Treatment Group
Mean (SD)[1B]	0.60 (1.23)	0.43 (0.95)	0 (0.91)	0.3 (1.7)	-0.48 (1.6)	-0.39 (1.9)
LS Mean (95% CI)[2]	0.60 (0.13, 1.06)	0.48 (0.04, 0.91)	0 (-0.5, 0.5)	0.55 (-0.3, 1.39)	-0.17 (-1, 0.62)	-0.34 (-1.2, 0.5)
p-value[3]	0.0141	0.0323	0.9907	0.1928	0.6613	0.4294
Comparison	Difference[4]	95% CI[5]	p-value[6]	Difference[4]	95% CI[5]	p-value[6]
Test vs. Placebo	0.12	-0.47, 0.70	0.6857	0.72	-0.16, 1.6	0.1040
Test vs. No treatment	0.59	-0.08, 1.26	0.0805	0.88	-0.13, 1.9	0.0844
Placebo vs. No Treatment	0.48	-0.17, 1.12	0.1429	0.16	-0.8, 1.14	0.7353

1A) Mean (SD) of differences from treatment baseline calculated for each subject as difference of Pre-treatment pain assessment after stimulus on tibio-femoral with post treatment pre-scan/post-treatment post-scan pain assessment after stimulus on tibio-femoral.
1B) Mean (SD) of differences from treatment baseline calculated for each subject as difference of Pre-treatment pain assessment after stimulus on patello-femoral with post treatment pre-scan/post-treatment post-scan pain assessment after stimulus on patello-femoral.
2) Treatment least square (LS) mean and 95% confidence intervals from ANCOVA using Proc mixed with period and baseline (NRS assessment during pre-screening in visit 1) as covariates and treatment as a factor.
3) p-value associated with T-test (H0: LS mean = 0).
4) Difference of LS means of first named treatment minus second named treatment.
5) 95% confidence intervals of difference between treatment LS means.
6) p-value from multiple comparisons of Proc Mixed.

Safety Results: There were a total of 8 adverse events (AEs) reported in the study by 6 subjects

	Test Group (N=29)		Placebo (N=28)		No Treatment (N=30)	
	N (%)	nAE	N (%)	nAE	N (%)	nAE
Number of subjects with at least one AE	3(10.3)	3	3(10.7)	3	2(6.7)	2
Anxiety	1(3.4)	1	1(3.6)	1	0	0
Claustrophobia	0	0	0	0	1(3.3)	1
Dental caries	1(3.4)	1	0	0	0	0
Diarrhoea	0	0	1(3,6)	1	0	0
Laceration	0	0	0	0	1(3.3)	1
Bone pain	1(3.4)	1	0	0	0	0
Headache	0	0	1(3.6)	1	0	0

Serious Adverse Events - On-Therapy : No serious adverse events (SAEs) occurred during this study