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.

Study No.: C7100991

Title: To Assess the Subjective Effect of Two Paracetamol Preparations on the Feeling of Breathing in Subjects with the Common Cold.

Rationale: The common cold is one of the most common human infections, with 100 million colds annually in the USA. Paracetamol has been shown to be more effective than placebo in treating symptoms associated with upper respiratory tract infection; sore throat, headache and fever. Menthol is often added to products for sufferers of cold and flu as it provides a pleasant sensation of increased nasal airflow. This current mentholated paracetamol hot drink combines paracetamol in a hot drink formulation with the added benefit of the menthol in the flavour system for perception of increased airflow. The aim of this study is to evaluate the degree to which this formulation will provide perception of relief of symptoms.

Phase: IV

Study Period: 4th October 2010 to 2nd December 2010

Study Design: This is a single centre, parallel, open label study with 2 arms.

Centre: 1, UK

Indication: Common cold

Treatments: (Timing of administration were considered to be the time that subjects are presented with product rather than when actually ingested)

Test Product

Mentholated paracetamol hot drink containing paracetamol 500 milligram (mg). Mineral water was poured into an empty kettle, which was then boiled. After the water had reached boiling temperature, approximately 200 mL of the hot water was poured into the mug and product sachet added, stirring for 10 seconds.

Reference Product

Paracetamol 500 mg tablet taken immediately with a measured 200 mL of ambient Volvic water, which was taken orally.

Objectives:

Primary Objective

To subjectively assess the feeling of breathing in people suffering from the common cold over a 15 minute period, following a dose of a mentholated paracetamol hot drink compared to baseline.

Secondary Objectives

- To subjectively assess the feeling of breathing in people suffering from the common cold over a 15 minute period, following a dose of a mentholated paracetamol hot drink compared to a single dose of paracetamol.
- To subjectively assess the feeling of breathing in people suffering from the common cold over a 60 minute period, following a dose of a mentholated paracetamol hot drink compared to baseline and to a single dose of paracetamol.
- To subjectively assess the relief of symptoms of common cold other than breathing difficulty in people suffering from the common cold over a 15 and 60 minute period, following a dose of a mentholated paracetamol hot drink compared to baseline and to a single dose of paracetamol.

Primary Efficacy Variables:

Mean Breathing Score over the first 15 minutes post product administration

Secondary Efficacy Variables:

- Breathing score over the 60-minute period.
- Score relating to cold symptoms other than breathing.
- How soothing the hot drink is and overall cold symptoms.

Statistical Methods:

The 11 symptom and product assessment questions(as mentioned below 1-11) were each rated using a 5 point visual rating scale (VRS), from 0 = strongly disagree to 4 = strongly agree, such that a high value represents a favourable score. The primary analysis was of the mean breathing score over the first 15 minutes post product administration. At each time-point (baseline, 30 seconds, 2, 5, 15, 30, 45 and 60 minutes post dose), a mean breathing score was calculated from questions 1, 3, 5, 7, 8 and 9 of the Symptoms and Product assessment. For each subject, a mean score was derived by summing the non missing responses and dividing by the number of questions answered. The subject level breathing score was analysed using a repeated measures analysis with an unstructured covariance matrix. The repeated measures model included treatment group and time as factors, and a term for the treatment by time interaction effect. The baseline score was adjusted for in the analysis by including the baseline assessment as part of the repeated measures series. Subject was the unit of analysis. The hypothesis testing was performed in two stages. Firstly, for the mentholated paracetamol hot drink group, the average effect over the first 15 minutes was compared to baseline. If this comparison achieved statistical significance ($p<0.05$), a comparison of the average effect over the first 15 minutes between the two treatment groups was then performed. For completeness, the average effect over the first 15 minutes compared to baseline for the paracetamol tablet group also performed.

The secondary analyses were done using the same repeated measures model as for the 15-minute period. At each time-point (baseline, 30 seconds, 2, 5, 15, 30, 45 and 60 minutes post dose), a mean score was calculated from questions 2, 4 and 6 (items relating to head feeling clear, soothing in throat and cough soothed) of the Symptoms and Product assessment. For each subject, a mean score was derived by summing the non-missing responses and dividing by the number of questions answered. The subject-level score was analysed using the same model as was used for the breathing score. Questions 10 and 11 of the Symptoms and Product assessment items were analysed separately over the 15-minute and 60-minute periods, using a repeated measures model with an unstructured covariance matrix. Treatment group and time were included as factors, and a term was included for the treatment by time interaction effect. Subject was the unit of analysis. Exploratory analyses were performed at pre-dose, the first 15-minute time period and the full 60-minute time period, using the 6 items (questions 1, 3, 5, 7, 8 and 9) contributing to the overall breathing score, as follows: In order to quantitatively assess the internal consistency of each of the 6 items (questions 1, 3, 5, 7, 8 and 9) contributing to the overall breathing score, Cronbach's coefficient alpha was calculated. Also, to determine how each item reflects the reliability of the scale, Cronbach's alpha coefficient was calculated after deleting each item independently from the scale.

After the reporting of the pre-planned statistical analyses, a further post-hoc analysis of the mean breathing score at each post-dose time-point during the primary time period (30 seconds, 2, 5 and 15 minutes) was considered of interest to aid interpretation of the study data. The objective of this post-hoc analysis was to ascertain the first time-point at which there was a statistically significant treatment effect, and for how long over the primary time period, the statistically significant difference was maintained (results given in Table 3). For this analysis, the significance level was adjusted to 1.25% (Bonferroni correction) to account for multiple comparisons.

1. My breathing feels easy
2. My head feels clear
3. I feel my airways are open
4. I feel soothing in my throat
5. I feel a cooling sensation in my nose
6. I feel my cough is being soothed
7. I can feel the air flowing to my lungs easily
8. My nose feels less blocked
9. I feel my breathing is comfortable
10. The hot drink is soothing (post drink only)
11. Overall, my cold symptoms are improved (post drink only)

Study Population:	
	Overall
Total Subjects Screened, N:	200
Randomised, N:	200
Completed The Study, n	200
Demographics (All Randomized Subjects)	
N Intent To Treat (ITT) population	200
Sex, n (%)	
Females: Males	128 (64.0): 72 (36.0)
Mean Age, years (SD)	20.0±1.92
Race, n (%) Asian Black or African American White	 10 (5.0) 3 (1.5) 187 (93.5)
Primary Efficacy Results : Analysis of Breathing Score in people suffering from the common cold over a 15 minute period, following a dose of a mentholated paracetamol hot drink compared to baseline.(Table 1)	
Secondary Efficacy Results: 1. Analysis of Breathing Score in people suffering from the common cold over a 15 minute period, following a dose of a mentholated paracetamol hot drink compared to a single dose of paracetamol.(Table1) 2. Analysis of Breathing Score in people suffering from the common cold over a 60 minute period, following a dose of a mentholated paracetamol hot drink compared to baseline and to a single dose of paracetamol. (Table1)	

Table 1

	Mentholated Paracetamol Hot Drink (N=100)	Paracetamol Tablet (N=100)	Hot Drink vs. Tablet
Baseline	1.22	1.19	
0 to 15 minutes			
Adjusted mean Versus Baseline [1]	0.83	0.11	0.72
95% CI	0.73, 0.93	0.01, 0.21	0.58, 0.86
P-Value	<0.0001	0.0333	<0.0001
0 to 60 minutes			
Adjusted mean Versus Baseline [1]	0.92	0.34	0.58
95% CI	0.81, 1.02	0.23,0.44	0.44, 0.72
P-Value	<0.0001	<0.0001	<0.0001

[1] Represents the difference between the adjusted mean during the post-dose period compared to the baseline value. A positive value represents an improvement.

3. Analysis of relief of symptoms of common cold other than breathing difficulty in people suffering from the common cold over a 15 and 60 minute period, following a dose of a mentholated paracetamol hot drink compared to baseline and to a single dose of paracetamol (Table 2)

Table 2

	Mentholated Paracetamol Hot Drink (N=100)	Paracetamol Tablet (N=100)	Hot Drink vs. Tablet
Baseline	1.06	1.08	
0 to 15 minutes			
Adjusted mean versus Baseline [1]	0.64	0.13	0.50
95% CI	0.52, 0.75	0.02, 0.25	0.36, 0.65
P-Value	<0.0001	0.0187	<0.0001
0 to 60 minutes			
Adjusted mean versus Baseline [1]	0.87	0.35	0.52
95% CI	0.76, 0.99	0.24,0.46	0.38, 0.67
P-Value	<0.0001	<0.0001	<0.0001

[1] Represents the difference between the adjusted mean during the post-dose period compared to the baseline value. A positive value represents an improvement.

Additional Analysis: Analysis of Breathing Score by Time-Point(ITT)

Table 3

	Pre-Dose	30 seconds	2 minutes	5 minutes	15 minutes
Mentholated Paracetamol Hot Drink					
N	100	100	100	100	100
Mean	1.22	1.76	1.91	2.08	2.38
Paracetamol Tablet					
N	100	100	100	100	100
Mean	1.19	1.20	1.22	1.34	1.50
Hot Drink vs. Tablet					
Difference [1]		0.57	0.69	0.74	0.89
98.75% CI [2]		0.39, 0.74	0.49, 0.89	0.54, 0.95	0.66, 1.11
P-value		<0.0001	<0.0001	<0.0001	<0.0001

Raw means presented at pre-dose; adjusted means presented at all other time-points.
[1] Difference is first named treatment minus second named treatment such that a positive value favours the first named treatment.
[2] Confidence intervals of 98.75% to adjust for multiple comparisons.

Safety Results: The study treatments were well tolerated. No adverse events were reported.