SINUTAB® (PARACETAMOL 500MG/ PSEUDOEPHEDRINE 30MG)

PROTOCOL NUMBER: A7801002

A COMMUNITY PHARMACY BASED INVESTIGATION IN THE SELF-MEDICATION AREA

EFFICACY AND SAFETY OF SINUTAB® [PARACETAMOL (500 MG) AND PSEUDOEPHEDRINE (30 MG)] ON SUBJECTS WITH NASAL CONGESTION ACCOMPANIED BY HEADACHE IN THE SETTING OF A COMMON COLD.

This was a randomized, double-blind, placebo-controlled, comparative, multi-center study in parallel groups between Sinutab® and placebo.

Indication Studied:	Nasal congestion with headache in the setting of a common cold
Developmental Phase of Study:	Phase 4
Study Initiation Date:	First Subject Enrolled**: 24 January 2007**
Study Completion Date:	Last Subject Completed**: 25 March 2008**
Status/Date:	Final 11 December 2008
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2. SYNOPSIS

INVESTIGATORS: Arnold Herman MD PhD, Gert Laekeman PhD

STUDY CENTER(S): 32

PUBLICATIONS (REFERENCE): None

STUDY INITIATION AND COMPLETION DATES: 24 January 2007 to 25 March 2008

PHASE OF DEVELOPMENT: Phase 4

STUDY OBJECTIVES:

Primary: To assess the effectiveness of Sinutab® on the symptom relief of nasal congestion and headache in subjects with a common cold.

Secondary:

- To assess the effectiveness of Sinutab® on the Major Symptom Complex (MSC) of common cold.
- To assess the effectiveness of Sinutab® on the symptom relief of individual signs and symptoms of common cold, including the ones belonging to the MSC.
- To assess the number of days lost at work or school.
- To assess the effect of Sinutab® on quality of life during daytime and at night.
- To assess the time-to-resolution of the common cold.
- To evaluate the overall safety of Sinutab®.

METHODOLOGY

STUDY DESIGN: A randomized, double blind, placebo-controlled, comparative, phase 4, and multi-center study in parallel groups of Sinutab® or placebo.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED):

Planned: 300 evaluable subjects

Enrolled: 451 subjects, excluding 4 subjects who enrolled twice

Dropouts: 21 subjects

Analyzed for efficacy: 321 evaluable subjects, 440 full analysis subjects

Analyzed for safety: 440 subjects

Four subjects were enrolled in the study twice. The data for the second inclusions were listed separately, and were not considered in the statistical analyses and tabulations.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects aged 18 years or older with common cold, who: were willing and able to comply with study procedures, did not have a history of hypersensitivity to any of the components of the study medication, were not using any medication(s) that could possibly interfere with the study treatment, did not have any important concurrent medical conditions, were not participating in another clinical trial, had not participated in a clinical trial in the previous 3 months, did not work for any company involved in this study, and had read and signed an Informed Consent form.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Table S1 shows the details on the study medication.

Table S1: Batch and Formulation Numbers

Study Drug	Dosage Form	Batch Number	Mat-no
Sinutab®	Tablets containing paracetamol 500 mg plus pseudoephedrine 30 mg	3008035	902800
Placebo	Dummy tablets (lactose)	3000055	901303

DURATION OF TREATMENT: 5 days.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: Not applicable.

CRITERIA FOR EVALUATION:

EFFICACY EVALUATIONS:

Subjects self-evaluated eight symptoms of common cold (nasal congestion, sore throat, headache, pressure around the eyes, runny nose, sneezing, coughing and malaise) each evening, using the 5-point Modified Jackson Subject Evaluation Scale (MJS).

Primary endpoint: Mean change from baseline in the sum of nasal congestion and headache sign/symptom scores during the treatment days (defined as the days from the first day with study medication to the last day with study medication, inclusive).

Secondary endpoints:

- Change from baseline in the mean MSC score (sum scores for nasal congestion, headache, sore throat, and pressure around the eyes) over the treatment days.
- Change from baseline in the mean individual sign/symptom score over the treatment days, for nasal congestion, headache, sore throat, and pressure around the eyes.

- The percentage of days of work or school lost for days during treatment with study medication only. Assessments from Day 1 (= Screening Day) were not considered in the evaluation.
- Day Quality of Life mean scores, by assessing interference with concentration on days during treatment with study medication only.
- Night Quality of Life mean scores, by assessing interference with sleep using assessments from nights on which the previous day involved treatment with study medication only.

PHARMACOKINETIC, PHARMACODYNAMIC, AND/OR OTHER EVALUATIONS: No pharmacokinetic or pharmacodynamic evaluations were performed.

SAFETY EVALUATIONS: Adverse events (AEs) and body temperature.

STATISTICAL METHODS:

The Full Analysis Set (FAS) was defined as all randomized subjects who took at least one dose of study medication and had baseline and any post-baseline data.

The Evaluable Subjects Set (ESS) was defined as all subjects in the FAS with no significant protocol violations, with at least 3 days of treatment, and who had taken at least 75% of the study medication during the days of treatment

The primary analysis was based upon the Evaluable Subjects Set (ESS). The primary endpoint was the mean change from baseline in the sum of nasal congestion and headache sign/symptom scores, averaged over treatment days. Efficacy analysis was also performed on the Full Analysis Set (FAS). Each separate treatment comparison was performed two-sided at the 5% significance level.

All efficacy endpoint analyses for which screening assessments had been carried out were performed by means of an analysis of covariance (ANCOVA), with treatment and center (pooled into five approximately equally sized strata) as factors and the corresponding baseline values as covariates.

The Mann-Whitney test was used to analyze the percentage of days lost at work or school on the days with study medication. Fisher's Exact test was used for the corresponding day-by-day analysis of the proportion of subjects who stayed at home on a particular day with study medication.

RESULTS

SUBJECT DISPOSITION AND DEMOGRAPHY:

Table S2 gives an overview of the subject disposition and the analysis sets.

Table S2: Subject disposition and analysis sets

Analysis set	Placebo	Sinutab®	Total
Planned number of evaluable subjects	150	150	300
Randomized *	228	223	451
Discontinued	17	4	21
Subjects in the Full Analysis Set (FAS)	219	221	440
Subjects in the safety set	219	221	440
Subjects in the Evaluable Subjects Set (ESS)	152	169	321

* The numbers given exclude the 4 subjects who were included twice.

Four subjects were included in the study twice. For these subjects, only the results of their first inclusion were used for the analyses.

Table S3 shows the demographic characteristics. The Sinutab® group contained slightly fewer male subjects than the Placebo group. The age, ethnic origin and oral temperature were equally distributed in the two treatment groups.

Table S3: Demographic characteristics

	ESS		FAS	
Variable	Placebo (N=152)	Sinutab® (N=169)	Placebo (N=219)	Sinutab® (N=221)
Age in years *	38.4 (11.44)	37.0 (11.78)	38.2 (11.59)	37.5 (11.73)
Gender (% male / % female)	48.0% / 52.0%	40.8% / 59.2%	44.3% / 55.7%	38.0% / 62.0%
Race (% white / % other)	98.0% / 2.0%	98.8% / 1.2%	98.6% / 1.4%	98.2% / 1.8%
Oral temperature in °C *	36.53 (0.669)	36.56 (0.612)	36.56 (0.634)	36.53 (0.639)

The four subjects included twice were only counted on the first occasion.

* Mean (standard deviation)

Table S4 shows the baseline values for the MSJ and Quality of Life scores. There were some differences in these scores between the Sinutab® group and the Placebo group. These differences between treatment groups were taken into account in the statistical analysis by using the baseline values of these scores as a covariate.

Table S4: Baseline values of MJS and Quality of Life scores

	ESS		FAS	
Variable *	**Placebo (N=152)**	**Sinutab® (N=169)**	**Placebo (N=219)**	**Sinutab® (N=221)**
Nasal congestion + headache (MJS score)	4.80 (1.128)	4.97 (1.136)	4.79 (1.109)	4.98 (1.160)
MSC (MJS score)	7.87 (2.254)	8.24 (2.080)	7.79 (2.212)	8.28 (2.153)
Nasal congestion (MJS score)	2.48 (0.746)	2.51 (0.708)	2.46 (0.737)	2.55 (0.722)
Headache (MJS score)	2.32 (0.715)	2.46 (0.673)	2.33 (0.692)	2.43 (0.714)
Sore throat (MJS score)	1.07 (1.011)	1.07 (0.955)	1.07 (0.997)	1.10 (1.009)
Pressure around the eyes (MJS score)	1.99 (1.058)	2.20 (0.955)	1.93 (1.051)	2.19 (0.974)
Interference with concentration	1.55 (1.133)	1.57 (1.004)	1.57 (1.079)	1.57 (1.071)
Interference with sleep	1.87 (1.259)	1.85 (1.116)	1.77 (1.247)	1.90 (1.161)

* Mean (standard deviation)

EFFICACY RESULTS:

Table S5 shows the mean change from baseline for the summed MJS scores of Nasal Congestion and Headache for the ESS. The MJS scores reduced during the study in both the Placebo group and the Sinutab® group. This is according with expectations. However, the mean reduction in MJS score was statistically significantly greater in the Sinutab® group than in the Placebo group.

Table S5: Mean change from baseline for MJS score for Nasal congestion + Headache in the ESS

Variable	**Placebo * N=152**	**Sinutab® * N=169**	**Estimated mean treatment difference †**	**P-value**
Mean change across treatment days	-1.82 (1.320)	-2.50 (1.247)	-0.56 (0.116)	<0.001

* Mean (standard deviation)

† Estimated mean treatment difference (standard error)

Table S6 shows the mean change from baseline for the MJS scores of the MSC, and of the four signs and symptoms that contribute to the MSC, for the ESS. As with the summed MJS scores for Headache and Nasal Congestion, the scores for the MSC and the individual signs and symptoms reduced during the study in both the Placebo group and the Sinutab® group. The mean reductions in MJS score were statistically significantly greater in the Sinutab® group than in the Placebo group for all scores considered.

Table S6: Mean change from baseline in MJS scores for MSC and MSC symptoms in the ESS

Sign or symptom	Placebo		Sinutab®		Estimated mean treatment difference †	P-value
	N*	Change in MSJ score**	N*	Change in MSJ score**		
MSC	151	-3.05 (2.274)	169	-4.19 (2.246)	-0.88 (0.206)	<0.001
Nasal congestion	152	-0.83 (0.698)	169	-1.11 (0.701)	-0.26 (0.066)	<0.001
Headache	152	-1.00 (0.788)	169	-1.39 (0.733)	-0.29 (0.065)	<0.001
Sore throat	151	-0.40 (0.705)	169	-0.52 (0.722)	-0.11 (0.050)	0.024
Pressure around the eyes	151	-0.82 (0.908)	169	-1.17 (0.830)	-0.22 (0.066)	0.001

* Number of subjects in this treatment group with non-missing data for this item
**Mean (standard deviation)

† Estimated mean treatment difference (standard error)

Table S7 shows the average Quality of Life scores for the ESS. These scores also reduced during the study in both the Placebo group and the Sinutab® group, indicating an improvement in the subjects' wellbeing. Sinutab® was significantly superior to Placebo at reducing interference with concentration during the day, but the difference between treatment groups for interference with sleep did not reach statistical significance.

Table S7: Quality of Life (QoL) scores in the ESS

Variable	Placebo		Sinutab®		Estimated mean treatment difference †	P-value
	N*	Change in QoL score**	N*	Change in QoL score**		
Interference with concentration	152	0.98 (0.731)	169	0.79 (0.583)	-0.21 (0.058)	<0.001
Interference with sleep	152	0.91 (0.677)	169	0.76 (0.767)	-0.14 (0.078)	0.066

Only the days on which study medication was taken were evaluated.

* Number of subjects in this treatment group with non-missing data for this item
**Mean (standard deviation)

† Estimated mean treatment difference (standard error)

Table S8 shows the number of days lost at work or school in the ESS. The numbers in both treatment groups showed the same pattern.

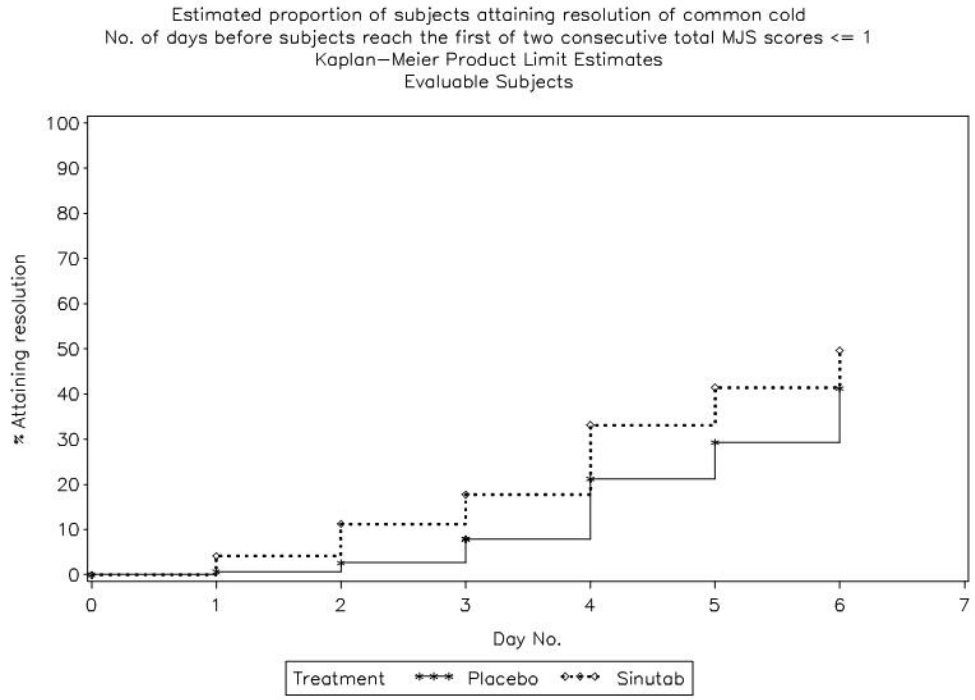
Table S8: Number of days lost at work or school in the ESS

Number of days lost	Placebo (N=152)	Sinutab® (N=169)
0	128 (84.2%)	150 (89.3%)
1	8 (5.3%)	7 (4.2%)
2	9 (5.9%)	8 (4.8%)
3	3 (2.0%)	0
4	2 (1.3%)	2 (1.2%)
5	2 (1.3%)	1 (<1.0%)
Total*	152 (100.0%)	168 (100.0%)

* Number of observations (percentage of total of subjects with non-missing data)

Figure S1 shows the Kaplan-Meier curve of the time to resolution in the ESS. There was a difference between treatment groups: resolution occurred earlier in the Sinutab® group than in the Placebo group.

Figure S1: Kaplan-Meier curve of time to resolution in the ESS



PHARMACOKINETIC, PHARMACODYNAMIC, AND/OR OTHER RESULTS:

No analyses were performed.

SAFETY RESULTS:

In general, Sinutab® was well tolerated. The most common AEs were fatigue (Sinutab® n=26, Placebo n=11), dizziness (S=21, P=6), nausea (S=19, P=8), myalgia, (S=7, P=11), sleep disorder (S=8, P=6), dry mouth (S=10, P=4), and upper abdominal pain (S=11, P=2). With the exception of myalgia, more subjects in the Sinutab® group reported these AEs than in the Placebo group. With the exception of fatigue and myalgia, the AEs listed are known side effects of pseudoephedrine. No subjects died during the study, and no serious AEs occurred. Two subjects in the Placebo group were withdrawn from the study due to an AE. Fifteen subjects in the Placebo group and four subjects in the Sinutab® group were withdrawn due to reasons other than an AE.

CONCLUSIONS:

- Sinutab® exerted a considerable beneficial effect on the summed MJS scores for Headache and Nasal Congestion in the ESS. The effect observed was statistically significant, compared to placebo. The results from the analyses in the FAS confirm those in the ESS.
- Sinutab® also exerted a considerable beneficial effect on the MJS scores for the MSC and the individual symptoms Headache, Nasal Congestion, Sore Throat and Pressure around the Eyes, and on the Quality of Life scores for Interference with Concentration in the ESS. The effects observed were statistically significant, compared to placebo. The results from the analyses in the FAS confirm those in the ESS. Sinutab® did not have a statistically significant treatment effect on the Quality of Life scores for Interference with Sleep in the ESS.
- Sinutab® did not have any statistically significant treatment effect on the number of days missed at work or school during treatment.
- Overall, these data demonstrate a positive treatment effect of Sinutab® on the symptom relief of nasal congestion and headache in subjects with a common cold
- Sinutab® was well tolerated.

REPORT DATE: 11 DECEMBER 2008