Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Webposting Clinical Trial Results Synopsis

Study Sponsor:	Bayer Consumer Care AG, Basel, Switzerland	
Study Number:	IMP11764	NCT 01062360
Study Phase:	3	
Study Title:	A pivotal, placebo controlled, phase III study to compare efficacy and tolerability of a fixed combination, containing 500 mg acetylsalicylic acid and 30 mg pseudoephedrine, in comparison to its single components in patients with sore throat and nasal congestion	
Therapeutic Area:	Nasal congestion and concomitant sore throat associated with upper respiratory tract infection (URTI)	
Name of Test Product:	Aspirin® Complex (500 mg acetylsalicylic acid in fixed combination with 30 mg pseudoephedrine)	
Active Ingredient:	Acetylsalicylic acid (ASA) and pseudoephedrine (PSE)	
Dosage:	Single oral dose of 1-2 Aspirin® Complex sachets, each containing granules of 500 mg ASA and 30 mg PSE	
Reference Therapy:	A) 500 mg ASA granules B) 30 mg PSE granules	
Dosage:	A single oral dose of 1-2 sachets of either treatment A or B	
Placebo:	Single dose 1 – 2 sachets , each containing placebo granules	
Route of Administration:	oral	
Treatment Duration:	as needed every 6 hours for not more than 3 days	
Study Period:	Date of first subjects' first visit:	20 Dec 2005
	Date of last subjects' last visit	14 May 2007
Methodology:	This was a 4-arm, multicenter, randomized, double-blind, placebo-controlled study in parallel groups who underwent a 2-hour in-patient period and a 3 day follow-up period.	
Study Site:	The study was conducted at 45 centers in Italy, 20 centers in Poland, 12 centers in Slovenia and 2 centers in the US.	
Main Inclusion Criteria:	1. Male and female subjects between 18 and 65 years of age. 2. Onset of cold symptoms within 96 hours (4 days) before study participation. 3. Current complaint of at least moderate sore throat at baseline, confirmed by a score of ≥ 6 on the sore throat pain scale (numerical 0 to 10 scale). 4. Current complaint of at least moderate NC at baseline, confirmed by a score of ≥ 6 on the NC scale (numerical 0 to 10 scale). 5. History of other symptoms associated with URTI during the last 4 days before study participation. 6. Other findings of URTI, confirmed on the physical examination. 7. Agreement to comply with the study requirements. 8. Written informed consent prior to enrollment in the study.	

Study Objectives:	<u>Overall:</u> This trial was designed to establish the superiority of the fixed combination of ASA 500 mg and PSE 30 mg (Aspirin® Complex, 2 sachets) versus ASA 500 mg (granules, 2 sachets) for the indication of nasal congestion, and to show the superiority of the fixed combination of ASA 500 mg and PSE 30 mg (Aspirin® Complex, 2 sachets) versus PSE 30 mg (granules, 2 sachets) for the indication of sore throat. <u>Primary:</u> Due to the nature of this study, 2 primary objectives were defined: <u>1) Nasal congestion:</u> The primary efficacy parameter to establish superiority for the indication of NC was the area under the time-concentration curve (AUC) calculated for baseline adjusted NC scores (NCS) for the initial 2 hours post-dosing, denoted as $AUC\text{-}NCS_{2\ hours}$ <u>2) Sore throat:</u> The primary efficacy parameter to establish superiority for the indication of sore throat was the sum of pain intensity differences over 2 hours ($SPID_{2\ hours}$), defined as the summed pain intensity difference over the initial observation period of 2 hours, weighted for the time between observations over 2 hours after administration of study drug. <u>Secondary:</u> • Safety and tolerability • Pain intensity differences from baseline at various time points up to 3 days post first dose • Total pain relief compared to baseline at various time points up to 3 days post first dose • Symptom-score of symptoms of common cold at various time points up to 3 days post first dose • Total dose used over the maximum period of 3 days Overall assessment of treatment, as given by subjects after 3 days post dose
Evaluation Criteria:	<u>Efficacy (Primary):</u> • The AUC calculated for baseline adjusted NCS for the initial 2 hours post-dosing, denoted as $AUC\text{-}NCS_{2\ hours}$. The $AUC\text{-}NCS_{2\ hours}$ was the area between line y = baseline NCS and observed subject's NCS during 2 hours calculated via the linear trapezoidal rule using real times of NCS assessments. • The $SPID_{2\ hours}$, which was the summed pain intensity difference over the initial observation period of 2 hours, weighted for the time between observations over 2 hours after administration of study drug. The $SPID_{2\ hours} = \Sigma\ PID_t \times$ [time (hours) elapsed since previous observation] where $PID_t = P_t - P_0$ and t is going until 2 hours (the $SPID_{2\ hours}$ was also indirectly adjusted to baseline pain intensity as pain intensity differences were used). <u>Efficacy (Secondary):</u> • The PID at time point: 15, 30, 60, 90, 120, 240, and 360 minutes after the first dose • The nasal congestion score at the same time points as described above • The nasal congestion relief score at the same time points as described above • Sore throat pain relief at the given time points • The symptoms of common cold (headache, sinus pressure/pain, feverish discomfort, muscle aches, and pain) at 120 minutes post-dose • The results of an overall assessment of treatment by the subjects at 120 minutes post-dose • The results of an overall assessment of treatment by the subjects at the end of Day 3 after the first dose, or at the end of treatment (6 hours after last dose of study drug) • The NCS at the end of Day 2 and at the end of Day 3, or at the end of treatment (6 hours after the last study drug intake) • The PID at the end of Day 2 and at the end of Day 3, or at the end of treatment (6 hours after the last study drug intake) • Sore throat pain relief at the end of Day 2 and at the end of Day 3, or at the end of treatment (6 hours after the last study drug intake) • The symptoms of common cold (headache, sinus pressure/pain, feverish discomfort, muscle aches, and pain) at the end of Day 2 and at the end of Day 3, or at the end of treatment (6 hours after the last study drug intake) • Total amount of drug intake.

	Safety • Exposure to study medication, i.e., number of study tablets used during the entire study period • Exposure to rescue medication, i.e., number of rescue tablets used during the entire study period • Time until first intake of rescue / disallowed medication • Adverse events recorded throughout the study period • Patient general physical condition, i.e., blood pressure, heart rate, body temperature Safety analyses were performed for all randomized patients who took at least one dose of study medication (Safety Set). Pharmacokinetics Not applicable
Statistical Methods:	Efficacy: The superiority of the combination ASA 1000 mg and PSE 60 mg (Aspirin® Complex) versus ASA 1000 mg for the indication nasal congestion assessed via the area under the curve (AUC) calculated for baseline adjusted nasal congestion score (NCS) for the initial 2 hours post-dosing ($AUC\text{-}NCS_{2\ hours}$) was inferentially tested by the unstratified Wilcoxon test (because there are many centers with less than or equal to 5 patients where the requirement of at least 2 patients per each active treatment arm is violated). The superiority of the combination ASA 1000 mg and PSE 60 mg (Aspirin® Complex) versus PSE 60 mg for the indication sore throat assessed via $SPID_{2\ hours}$ (the sum score of the time adjusted pain intensities over 2 hours after administration of study drug) was inferentially tested by the unstratified Wilcoxon test. Both null hypotheses had to be rejected to show efficacy of the combination drug Aspirin® Complex. Therefore, an adjustment of the significance level due to multiplicity was not necessary. Due to one-sided tests, the level of significance was set to 0.025 (2.5%) for both one-sided hypotheses defined above. The confirmatory analysis was performed for the full analysis set. All other treatment arm differences were determined and tested on an exploratory basis only. All items recorded in the case report form (CRF) were analyzed by means of descriptive statistical methods. Whenever appropriate, standard summary statistics (number of non-missing observations, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum) were calculated. Categorical data (eg, gender, ethnic origin) were summarized in frequency tables. All items were analyzed by treatment group. Safety All safety data were summarized by treatment group and listed in detail. Pharmacokinetics Not applicable
Number of Subjects:	Planned: 984 Screened: 1020 Randomized: 1016 Treated: 1015 (568 female and 447 male subjects) Aspirin® Complex, 253; ASA, 250; PSE, 251; placebo, 261 Prematurely terminated: 34 Completed: 981 Analyzed (safety): 1015 (568 female and 447 male subjects) Analyzed (efficacy): 1015 (full analysis set [FAS]); 989 (per-protocol set I [PPSI]); 916 (per-protocol set II [PPSII]) Aspirin® Complex: 253 (FAS), 249 (PPSI), 235 (PPSII); ASA: 250 (FAS), 244 (PPSI), 223 (PPSII); PSE: 251 (FAS), 245 (PPSI), 229 (PPSII); Placebo: 261 (FAS), 251 (PPSI), 229 (PPSII)

Results Summary — Subject Disposition and Baseline

	Total	Aspirin-PSE	Aspirin	PSE	Placebo
screened	1020	---	---	---	---
randomized	1016	253	250	251	262
treated	1015	253	250	251	261
completed	981	247	239	243	252

	Aspirin-PSE	Aspirin	PSE	Placebo	Total
N	253	250	251	261	1015
Age, mean (SD)	35.6 (11.93)	36.2 (12.25)	36.5 (12.11)	38.6 (12.54)	36.7 (12.24)
Gender, %, male / female	46.6 / 53.4	40.8 / 59.2	41.8 / 58.2	46.7 / 53.3	44.0 / 56.0
Race, caucasion in %	99.2	98.4	98.8	100	99.1
Weight, kg, mean (SD)	73.2 (17.22)	70.5 (15.30)	71.1 (15.64)	70.5 (15.46)	71.3 (15.94)
Height, cm, mean (SD)	171.2 (9.06)	170.0 (9.99)	169.9 (8.54)	170.3 (9.31)	170.3 (9.24)
BMI, kg/m2, mean (SD)	24.8 (4.67)	24.3 (4.40)	24.5 (4.52)	24.1 (3.88)	24.4 (4.38)

Results Summary — Efficacy

Primary objectives

AUC-$NCS_{2\ hours}$

For the FAS using LOCF/LIM imputation (FAS LOCF/LIM), the median AUC-$NCS_{2\ hours}$ was 2.00 for Aspirin® Complex and 1.81 for ASA. The difference between these 2 treatments was not statistically significant (point estimate of difference, 0.25; Hodges-Lehmann 95% confidence interval [CI], 0.00 to 0.75; p = 0.0367). For the FAS using observed cases (FAS OC), the median AUC-$NCS_{2\ hours}$ was also 2.00 for Aspirin® Complex and 1.81 for ASA, and the treatment difference between the 2 treatments was not statistically significant (point estimate of difference, 0.25; CI, 0.00 to 0.75; p = 0.0367). For the PPSI, the median AUC-$NCS_{2\ hours}$ was 2.00 for Aspirin® Complex and 1.88 for ASA, and the treatment difference between the 2 treatments was not statistically significant (point estimate of difference, 0.25; CI, 0.00 to 0.75; p = 0.0480). For the PPSII, the median AUC-$NCS_{2\ hours}$ was 2.00 for Aspirin® Complex and 1.75 for ASA, but in this analysis the difference between the 2 treatments was statistically significant (point estimate of difference, 0.38; CI, 0.00 to 0.75; p = 0.0226).

Exploratory analysis of the FAS LOCF/LIM for treatment differences in AUS-$NCS_{2\ hours}$ between other treatment pairs (Aspirin® Complex and PSE, Aspirin® Complex and placebo, ASA and placebo, and PSE and placebo) revealed no statistically significant difference for any treatment pair. However, for Aspirin® Complex and placebo, the point estimate of difference (CI) was 0.25 (0.00,0.75) (p = 0.0371), whereas for ASA and placebo, it was 0.00 (-0.25, 0.25) (p = 0.5297). Exploratory analysis of the FAS OC, PPSI, and PPSII produced similar results.

$SPID_{2\ hours}$

For the FAS LOCF/LIM, the median $SPID_{2\ hours}$ was 2.00 for both Aspirin® Complex and PSE. There was no statistically significant difference between these 2 treatments (point estimate of difference, 0.00; CI, 0.00 to 0.50; p = 0.1342). Analysis of the FAS OC provided similar results. For the PPSI, the median $SPID_{2\ hours}$ was 2.00 for both Aspirin® Complex and PSE, and there was no statistically significant difference between the 2 treatments (point estimate of difference, 0.00; CI, 0.00 to 0.50; p = 0.1213). For the PPSII, the median $SPID_{2\ hours}$ was 2.00 for Aspirin® Complex and 1.75 for PSE and there was again no statistically significant difference between the 2 treatments (point estimate of difference, 0.00; CI, 0.00 to 0.50; p = 0.1003).

Exploratory analysis of the FAS LOCF/LIM for differences in $SPID_{2\ hours}$ between other treatment pairs (Aspirin® Complex and ASA, Aspirin® Complex and placebo, ASA and placebo, and PSE and placebo) revealed a statistically significant difference for one of the pairs: Aspirin® Complex and placebo. In that analysis, the point estimate of difference (CI) was 0.25 (0.00, 0.75) (p = 0.0230). Exploratory analysis of the FAS OC, PPSI, and PPSII produced similar results.

Secondary objectives

Secondary exploratory efficacy analyses demonstrated that Aspirin® Complex had a beneficial treatment effect on several secondary efficacy variables (NCS, NC relief, PID, sore throat pain relief, and the common cold symptoms of headache and feverish discomfort) at several time points.

Results Summary — Pharmacokinetics

Not applicable

Results Summary — Safety

No deaths occurred during the study. One subject experienced a serious adverse event (acute appendicitis) during treatment with Aspirin® Complex that was not considered related to the study drug. Overall, 137 of 1015 subjects (13.5%) in the safety set reported AEs. The incidence of AEs was similar among the subjects who received Aspirin® Complex (36/253; 14.2%), ASA (33/250; 13.2%), PSE (34/251; 13.5%), and placebo (34/261; 13.0%). A total of 26/1015 subjects (2.6%) permanently discontinued the study drug due to an AE: 3/253 subjects (1.2%) during treatment with Aspirin® Complex, 9/250 subjects (3.6%) during treatment with ASA, 9/251 subjects (3.6%) during treatment with PSE, and 5/261 subjects (1.9%) during treatment with placebo. A total of 66/1015 subjects (6.5%) experienced AEs that were considered significant (ie, some action was taken with regard to the AE): 11/253 subjects (4.3%) during treatment with Aspirin® Complex, 18/250 subjects (7.2%) during treatment with ASA, 19/251 subjects (7.6%) during treatment with PSE, and 18/261 subjects (6.9%) during treatment with placebo.

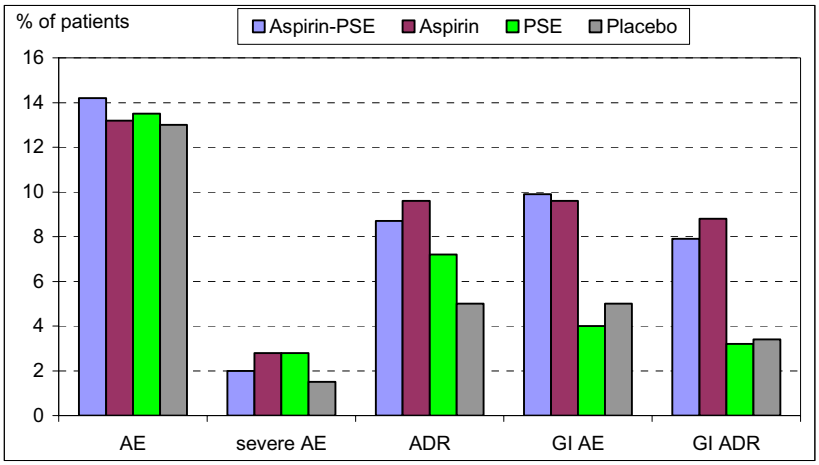
Gastrointestinal disorders represented the system organ class with the highest incidence of AEs overall (72/1015 subjects; 7.1%) and within each treatment group (25/253 subjects [9.9%] during treatment with Aspirin® Complex, 24/250 subjects [9.6%] during treatment with ASA, 10/251 subjects [4.0%] during treatment with PSE, and 13/261 subjects [5.0%] during treatment with placebo). Nervous system disorders were reported by 29/1015 subjects (2.9%) overall and by 4/253 subjects (1.6%) during treatment with Aspirin® Complex, 3/250 subjects (1.2%) during treatment with ASA, 11/251 subjects (4.4%) during treatment with PSE, and 11/261 subjects (4.2%) during treatment with placebo. The AEs experienced by ≥ 1% of subjects overall were nausea (2.8%), dyspepsia (2.3%), headache (2.0%), abdominal pain (1.0%), and diarrhoea (1.0%).

For each study treatment, most AEs were of mild or moderate intensity. Severe AEs were experienced by 5/253 subjects (2.0%) who received Aspirin® Complex, 7/250 subjects (2.8%) who received ASA, 7/251 subjects (2.8%) who received PSE, and 4/261 subjects (1.5%) who received placebo.

Drug-related AEs were experienced by 22/253 subjects (8.7%) who received Aspirin® Complex, 24/250 subjects (9.6%) who received ASA, 18/251 subjects (7.2%) who received PSE, and 13/261 subjects (5.0%) who received placebo. Drug-related AEs experienced by ≥ 1% of subjects overall were nausea (2.3%), dyspepsia (2.3%), and abdominal pain (1.0%). Drug-related AEs experienced by ≥ 1% of subjects who received Aspirin® Complex were nausea (3.6%) and dyspepsia (3.2%). These AEs are well-known and documented side effects of ASA.

No clinical laboratory evaluations were performed during the course of this trial.

		Aspirin-PSE	Aspirin	PSE	Placebo
Aspirin-PSE N=253	AE	14.2	13.2	13.5	13.0
Aspirin N=250	severe AE	2.0	2.8	2.8	1.5
PSE N=251	ADR	8.7	9.6	7.2	5.0
Placebo N=261	GI AE	9.9	9.6	4.0	5.0
	GI ADR	7.9	8.8	3.2	3.4



Conclusion(s)

- As shown by primary efficacy analyses, Aspirin® Complex (2 sachets) was not superior to ASA 500 mg (granules, 2 sachets) for the indication of NC.
- As shown by primary efficacy analyses, Aspirin® Complex (2 sachets) was not superior to PSE 30 mg (granules, 2 sachets) for the indication of sore throat.
- As shown by secondary efficacy analyses, Aspirin® Complex (2 sachets) had a beneficial treatment effect on NCS, NC relief, sore throat pain relief, PID, and the common cold symptoms of headache and feverish discomfort.
- As shown by safety analyses, Aspirin® Complex (2 sachets) was safe and well tolerated for the treatment of subjects with sore throat and NC associated with URTI.

Publication(s)

Not planned

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