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.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG, Consumer Care	
Study Number:	13700	NCT00963443 EudraCT: 2009-011355-46
Study Phase:	III	
Official Study Title:	A double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of acetylsalicylic acid combined with pseudoephedrine, compared with acetylsalicylic acid alone, and pseudoephedrine alone, on symptoms of pain and nasal congestion in patients with symptomatic upper respiratory tract infection	
Therapeutic Area:	Upper Respiratory Tract Infection/ cough and cold	
Test Product		
Name of Test Product:	Acetylsalicyclic Acid + pseudoephedrine (Aspirin® Complex, BAYE4465)	
Name of Active Ingredient:	Acetylsalicylic acid and pseudoephedrine	
Dose and Mode of Administration:	Treatment A - 1000 mg acetylsalicylic acid (ASA) plus 60 mg pseudoephedrine (PSE) (2 sachets of 500 mg ASA plus 30 mg PSE). Sachets were to be taken orally after dissolving in a glass of water (approximately 200 ml) with a minimum interval of 6 hours. The treatment was to be taken 2-3 times on Day 1 and 3 times daily on Day 2 and on Day 3.	
Reference Therapy/Placebo		
Reference Therapy:	Treatment B - 1000 mg ASA (2 sachets of 500 mg ASA) Treatment C - 60 mg PSE (2 sachets of 30 mg PSE) Treatment D- Matching Placebo (2 sachets of placebo)	
Dose and Mode of Administration:	Sachets were to be taken orally after dissolving in a glass of water (approximately 200 ml) with a minimum interval of 6 hours. All treatments were to be taken 2-3 times on Day 1 and 3 times daily on Day 2 and on Day 3.	

Duration of Treatment:	The duration of treatment for each patient was three days.	
Studied period:	Date of first subjects' first visit:	15 Sep 2009
	Date of last subjects' last visit:	26 Mar 2012
Premature Study Suspension / Termination:	Not applicable.	
Substantial Study Protocol Amendments:	The study was conducted according to Study protocol latest version from 18 Apr 2011, and included no substantial amendments.	
Study Centre(s):	1 center in the United Kingdom	
Methodology:	The trial consisted of two visits to the site. At the first visit (Day 1), patients were screened for entry to the study. Eligible patients were randomized in a 2:2:2:1 ratio to receive a single dose consisting of 2 sachets of one of the four treatment regimens; either the combination product (Treatment group A), acetylsalicylic acid (Treatment group B), pseudoephedrine (Treatment group C) or placebo (Treatment group D) in chronological order that they were enrolled. Assessments of nasal airflow and subjective scores for pain and nasal congestion were made at the site prior to dosing and at 1, 2, 3 and 4 h after treatment. A second dose was to be taken at home at least 6 h after the first dose taken at the clinic. A third dose was to be taken in the evening of Day 1 if there was a minimum interval of 6 h since the second dose. Patients were encouraged to take the study medication on Days 2 and 3 at 9 am ± 1 h, at 3 pm ± 1 h and at 9 pm ± 1 h. Every evening before the last dose patients were to assess nasal congestion and pain by using various Categorical Rating Scale (CRS). In the evening of Day 3, patients also completed the global assessments of pain relief and congestion relief. Patients returned to the site for a follow-up (FU) within 8 days after receiving the initial dose and any adverse events (AEs) and use of concomitant medications were recorded since the initial visit.	
Indication/ Main Inclusion Criteria:	Upper Respiratory Tract Infection Male and female subjects in general good health with suspected viral upper respiratory tract infection (common cold), aged at least 18 years, were eligible to participate in the trial.	
Study Objectives:	<u>Overall:</u> To compare the efficacy of acetylsalicylic acid (ASA) / pseudoephedrine (PSE) combination in common cold, with ASA alone and with PSE alone and with placebo. <u>Primary:</u> To compare the efficacy of 1000 mg ASA combined with 60 mg PSE for pain and nasal congestion with 1000 mg ASA alone, 60 mg PSE alone and placebo in patients with symptomatic common cold caused by acute upper respiratory tract infection (URTI) for the initial 4 hours after first dose.	

	Secondary: •Area under the curve for nasal airflow conductance from baseline •Sum of subjective nasal congestion intensity differences (SNCID) •Total subjective nasal congestion relief (TNCR) •Global assessment of nasal congestion relief •Sum of pain intensity differences (SPID) •Total pain relief (TOTPAR) •Global assessment of pain relief •Safety and tolerability
Evaluation Criteria:	Efficacy (Primary): Two primary endpoints were defined. Both endpoints were to be met. If this was shown, it could be concluded that the combination product was superior to its single components. The primary efficacy variables were: •Nasal airflow conductance as the area under the nasal airflow conductance curve 0-4 h post-dose (AUC0-4h) •Total pain relief (TOTPAR), measured with a 5 point composite CRS (composite of sore throat pain and headache pain) over 4 h post-dose (TOTPAR0-4h) Efficacy (Secondary): The secondary efficacy variables were: •Area under the curve for nasal airflow conductance from Baseline to 1 h (AUC0-1h) •Area under the curve for nasal airflow conductance from Baseline to 2 h (AUC0-2h) •Area under the curve for nasal airflow conductance from Baseline to 3 h (AUC0-3h) •Sum of subjective nasal congestion intensity differences (SNCID) for the time-period 0-4 h •Sum of SNCID for the time period 0-3 days •Total subjective nasal congestion relief (TNCR) for the time-period 0-4 h •TNCR for the time-period 0-3 days •Global assessment of nasal congestion relief at the evening of Day 3 •Sum of pain intensity differences (SPID) for the time-period 0-4 h •SPID for the time period 0-3 days •TOTPAR for time period 0-3 days •Global assessment of pain relief at the evening of Day 3 Safety: The safety variables were: •Adverse events (AEs)

	•Serious adverse events (SAEs) •Physical examination, including vital signs
Statistical Methods:	Efficacy (Primary): In order to protect the overall type 1 error at the 0.05 level, the hierarchical testing procedure was conducted in the following order (Note: The order of testing not only took into account the order of interest, but also the likelihood of attaining significant results). 1. Reduction of nasal congestion; 2. Relief of pain Analysis of Variance (ANOVA) was used to test for treatment differences, and included treatment as a fixed effect. Although other pair-wise comparisons were made in order to present the complete efficacy profile, the primary treatment comparison was made between: • ASA plus PSE and ASA for reduction of nasal congestion • ASA plus PSE and PSE for relief of pain Once a pair-wise comparison was statistically non-significant at the level of 0.05, the subsequent comparisons were to be technically ineligible to be declared significant. However, all pair-wise comparisons were presented to provide a complete clinical picture. Least squares (LS) means for each treatment and the mean differences between treatments were calculated and presented, along with the associated 95% confidence intervals (CI) and p-values. *Normality assumption checking* Based on the fitted ANOVA model for the observed primary endpoint, the Shapiro-Wilk test statistic, (W), for testing the hypothesis of normality was calculated for the Studentised residuals. The test statistic, W, and plots of the studentised residuals were visually checked for the assumption of normality. In the event that normality was revealed to be unreasonable, the data was log transformed. Again using the Shapiro-Wilk test statistic and plots of the studentised residuals, if the assumptions of normality were revealed still to be unreasonable then an alternative transformation or analysis method was sought. The assumption of normality was not satisfied and log transformation did not help with normality. Hence, a Mann-Whitney U-test was used to test each treatment pair-wise comparison in addition to the ANOVA and the focus of the results is on the Mann-Whitney U-test results. P-values for each treatment pair-wise comparison were calculated and presented. Efficacy (Secondary): Each parameter was tested for treatment differences, and included treatment as a fixed effect. Although all pair-wise comparisons were made in order to present the complete efficacy profile, the primary treatment comparison was made between - ASA plus PSE and ASA

	Safety: Safety data was summarised using descriptive statistics
Number of Subjects:	Planned - A total of 822 evaluable patients were required for the trial. Assuming a drop out rate of about 6%, approximately 875 patients were to be randomized into the trial in order to achieve 822 evaluable patients. It was expected that approximately 1050 patients were to be screened. Analyzed - A total of 833 patients were randomised into the study from a single site in the UK. Of these, 235 patients were randomised to the ASA/PSE combination group, 240 patients to the ASA alone group, 237 patients to the PSE alone group and 121 patients to the placebo group. All these 833 randomised patients were treated.

Study Results

Results Summary — Subject Disposition and Baseline

A total of 833 patients were randomised into the study from a single site in the UK. Of these, 235 patients were randomised to the ASA/PSE combination group, 240 patients to the ASA alone group, 237 patients to the PSE alone group and 121 patients to the placebo group. All these 833 randomised patients were treated.

Following randomization, a total of 827 out of 833 patients (99.3%) completed the study: 232 out of 235 patients (98.7%) who received ASA/PSE combination, 239 out of 240 patients (99.6%) who received ASA alone, and 235 out of 237 patients (99.2%) who received PSE alone. All the 121 patients randomised to placebo group completed the study.

Overall, a small number of patients (6 out of 833 patients [0.7%]) discontinued the study prematurely. Of these, 3 out of 235 patients (1.3%) were from ASA/PSE combination group, 1 out of 240 patients (0.4%) was from the ASA alone group and 2 out of 237 patients (0.8%) were from the PSE alone group. The majority of the patients (4 out of 6 patients [0.5%]) discontinued due to withdrawal of consent followed by 2 out of 6 patients (0.2%) that were lost to FU

Overall, the demographics of the ASA/PSE combination, ASA alone, PSE alone and placebo groups were comparable.

Overall, the majority of patients were female (561 out of 829 [67.7%]) compared to the male patients (268 out of 829 [32.3%]).

The majority of patients were white (775 out of 829 [93.5%]), with 35 out of 829 (4.2%) Asian, 12 out of 829 (1.4%) of other race, 5 out of 829 (0.6%) black, and 2 out of 829 (0.2%) hispanic. There was a similar distribution of race between the treatment groups.

Overall, the mean age of the patients was 20.0 years (range: 18 to 39 years), and was similar across the treatment groups.

Overall, the mean weight of the patients was 68.62 kg (range 43.0 to 117.2 kg). The mean weight of patients was similar across the treatment groups.

Overall, the mean BMI of the patients was 23.861 kg/m2 (range: 16.69 to 41.34 kg/m2). The mean BMI of patients was similar across treatment groups.

Of the 833 patients in the Safety population, four did not have at least one post-baseline efficacy assessment. Therefore, a total of 829 patients were included in the ITT Population.

Results Summary — Efficacy

The difference in mean primary efficacy endpoints of reduction of nasal congestion (AUC0-4h) and relief of pain (TOTPAR0-4h) were statistically significant for this study between ASA/PSE combination and ASA alone groups ($p<0.001$) and between ASA/PSE combination and PSE alone groups ($p=0.019$), respectively for AUC0-4h and TOTPAR0-4h. The primary treatment comparison was: ASA/PSE combination and ASA alone groups for reduction of nasal congestion and ASA/PSE combination and PSE alone groups for relief of pain.

This meant a lesser nasal resistance and a higher total pain relief score over 4 h post dose for patients on ASA/PSE combination compared to patients on PSE alone, ASA alone and placebo groups.

Similar results were observed following statistical analysis of the PP population.

Sensitivity analysis performed for patients with full profiles in the ITT populations also showed similar statistically significant results for these groups.

Secondary Efficacy Endpoints:

For the ITT population, the difference in nasal airflow conductance from Baseline to 1 h (AUC0-1h), 2 h (AUC0-2h) and 3 h (AUC0-3h), was statistically significant between the treatment comparison of ASA/PSE combination and ASA alone groups ($p<0.001$). This suggested a better nasal airflow conductance for patients in ASA/PSE combination.

The difference in SNCID0-4h and SNCID0-3D was not statistically significant between the treatment comparisons of ASA/PSE combination and ASA alone groups. The SNCID0-4h and SNCID0-3D versus time profile showed a greater decrease in the nasal congestion for ASA/PSE combination and PSE alone groups at each post dose time point compared to ASA alone and placebo groups.

The difference in TNCR0-4h and TNCR0-3D was statistically significant between the treatment comparison of ASA/PSE combination and ASA alone groups for nasal congestion relief ($p<0.001$ and $p=0.016$, respectively). The TNCR0-4h and TNCR0-3D versus time profile showed a greater increase in the nasal congestion relief for ASA/PSE combination and PSE alone groups at each post dose time point compared to ASA alone, and placebo groups.

The global assessment of nasal congestion relief at Day 3 was statistically significantly different between the treatment comparison of ASA/PSE combination and ASA alone groups ($p=0.040$).

The difference in SPID0-4h and SPID0-3D was not statistically significant between ASA/PSE combination and PSE alone groups. The pain intensity versus time profile (0-4 h and 3 Days) showed a greater decrease in the pain symptoms for ASA/PSE combination and ASA alone groups at each post dose time point compared to PSE alone and placebo groups.

The difference in TOTPAR0-3D was not statistically significant between ASA/PSE combination and PSE alone groups. The pain relief versus time profile (0-3 days) showed a reduction of pain symptoms to some relief (score=2) at Day 3 across all treatment groups.

The global assessment of pain relief at the evening of Day 3 was statistically significantly different between the treatment comparison of ASA/PSE combination and PSE alone groups ($p=0.043$).

Results Summary — Safety

The ASA/PSE combination was well tolerated in patients with symptomatic URTI.

A total of 37 out of 235 patients (15.7%) from ASA/PSE combination group experienced at least one TEAE with a comparable proportion of patients for the ASA alone group (27 out of 240 patients with TEAEs [11.3%]), PSE alone (28 out of 237 patients with TEAEs [11.8%]) and placebo groups (14 out of 121 patients with TEAEs [11.6%]). TEAEs considered related to the study treatment were experienced by 15 out of 235 patients with TEAEs (6.4%) in the ASA/PSE combination group, 13 out of 240 patients with TEAEs (5.4%) in ASA alone group, 8 out of 237 patients with TEAEs (3.4%) in PSE alone group and 4 out of 121 patients with TEAEs (3.3%) in the placebo group.

The most frequently reported treatment related TEAE across all the treatment groups was for the system organ class (SOC) of gastrointestinal disorders (27 out of 40 patients with TEAEs [67.5%]) and the most frequently reported TEAE as per PT was nausea (15 out of 40 patients with TEAEs [37.5%]) and dyspepsia (2 out of 40 patients with TEAEs [5.0%]). Nausea and dyspepsia were slightly more frequently reported from patients in ASA/PSE combination group (6 out of 15 patients with TEAEs [40.0%]for nausea and 1 out of 15 patients with TEAEs [0.66%] for dyspepsia) compared to ASA alone (5 out of 13 patients with TEAEs [38.46%] for nausea and 1 out of 13 patients with TEAEs [0.76%] for dyspepsia), PSE alone (3 out of 8 patients with TEAEs [37.5%] for nausea) and placebo groups (1 out of 4 patients with TEAEs [25.0%] for nausea).

Across all treatment groups, the majority of the number of patients with TEAEs reported were mild (56 out of 106 patients [52.8%]) or moderate (45 out of 106 patients [42.4%]). The number of patients who reported mild TEAEs were more from PSE alone group (20 out of 28 patients with TEAEs [71.4%]) compared to ASA alone (11 out of 27 patients with TEAEs [40.7%]) and placebo groups (9 out of 14 patients with TEAEs [64.3%]), and slightly more compared to ASA/PSE combination group (16 out of 37 patients with TEAEs [43.2%]). The number of patients who reported moderate TEAEs were more from ASA/PSE combination group (21 out of 37 patients with TEAEs [56.8%]) compared to ASA alone (14 out of 27 patients with TEAEs [51.9%]), PSE alone (7 out of 28 patients with TEAEs [25.0%]) and placebo groups (3 out of 14 patients with TEAEs [21.4%]).

A total of 22 out of 106 patients with TEAEs (20.8%) reported severe TEAEs as assessed by the Investigator. The most frequently reported severe TEAEs were of nausea (5 out of 22 patients with TEAEs [22.72%) and headache (2 out of 22 patients with TEAES [9.09%]).

No unexpected AE occurred. No patient was withdrawn from the study due to an AE. Overall, the majority of the patients (92 out of 106 patients with TEAEs [86.8%]) resolved without sequelae. A small number of patients with TEAEs (15 out of 106 patients with TEAEs [14.2%]) reported ongoing TEAEs at the final study visit. No death was reported in the study.

There was one event leading to two SAEs being captured (dizziness and fall) in one patient (ASA/PSE combination group), which were considered not related to the study treatment.

There were no apparent changes in the vital signs and physical examinations across all the treatment groups from Screening to FU.

Conclusion(s)

•The primary objective of this study to compare the efficacy of ASA/PSE combination for pain and nasal congestion with ASA alone, PSE alone and placebo in patients for the initial 4 h after first dose was met, with statistically significant differences between ASA/PSE combination and ASA alone ($p<0.001$) and between ASA/PSE combination and PSE alone ($p=0.019$) for the AUC0-4h and TOTPAR0-4h.

•These finding were supported by statistically significant results of secondary efficacy endpoints of nasal airflow conductance from Baseline to 1 h, 2 h and 3h, TNCR0-4h and TNCR0-3D, global assessments of nasal congestion relief and pain relief at Day 3 for ASA/PSE combination against ASA alone and PSE alone groups.

•ASA/PSE combination was well tolerated in patients with symptomatic URTI, with a relatively small number of TEAEs being reported across all treatment groups. No unexpected AE occurred.

Publication(s):	None		
Date Created or Date Last Updated:	7-Feb-2013	Date of Clinical Study Report:	11-Oct-2012

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Bayer Advanced Aspirin – Regular Strength Bayer Advanced Aspirin – Extra Strength
Brand/Trade Name(s) ex-US	New Aspirin® (Germany and Italy)
Generic Name	Aspirin
Main Product Company Code	BAY1019036
Other Company Code(s)	BAY-E4465 (Bayer internal code)
Chemical Description	2-acetoxybenzoic acid
Other Product Aliases	Acetylsalicylic acid Fast-release aspirin

Date of last Update/Change: 5 Aug 2014