Summary of results

Efficacy and tolerability of EPs® 7630 solution in patients (≥18 years old) with Acute Rhinopharyngitis (ARP)

A multicentre, randomized, double-blind, placebo-controlled, phase III clinical trial

Results of the final analysis
Study No. 701004.01.004
EudraCT No. 2007-005579-33

Date of report: 08 February 2017

First subject included: 05 January 2009
Last subject completed: 11 June 2009
Clean data: 14 December 2009
Decision on study completion: July 2010

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SUMMARY

Sponsor: Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany

Study title: Efficacy and tolerability of EPs® 7630 solution in patients (≥ 18 years old) with Acute Rhinopharyngitis (ARP): a multicentre, randomized, double-blind, placebo-controlled, phase III clinical trial.

Trial sites: The study was conducted in 19 study centres in Bulgaria.

Study period: First subject included: 05 January 2009
Last subject completed (for interim analysis): 11 June 2009
Clean data: 14 December 2009
Decision on study completion: July 2010

Publications: None

Clinical phase: III

Objectives: To evaluate the efficacy and tolerability of EPs® 7630 solution in patients (≥18 years old) with acute rhinopharyngitis (ARP)

Methodology: The study was conducted as a randomized, double-blind, placebo-controlled, multicentre clinical trial with 2 parallel treatment groups. Patients were randomized at day 1 to receive either EPs® 7630 solution or placebo for ten days. The primary outcome variable was the area under the curve (AUC) of the total score of rhinopharyngitis-relevant symptoms (RPS) from baseline (day 1, visit 1) to day 5 (visit 3).

Number of subjects included in the interim analysis:

	Planned to be randomized	Patients taken into account for the interim analysis				
				Safety	Efficacy	
		Included into screening	Randomized	Safety set	Full analysis set	Per protocol set
EPs® 7630	100		101	101	101	83
Placebo	100		100	100	100	85
All	200	201	201	201	201	168

Diagnosis and main criteria for inclusion:

Patients included were men or women (≥ 18 years old) with a diagnosis of acute rhinopharyngitis who gave written informed consent before inclusion. In order to be eligible for trial participation, patients had to have either

- both major rhinopharyngitis-relevant symptoms (RPS) (nasal discharge and sore throat) rated with ≥ 2 points each and at least two minor RPS (nasal congestion, sneezing, scratchy throat, hoarseness, cough, headache, muscle aches, or fever) rated with ≥ 2 points each or
- one major RPS rated with ≥ 2 points and at least three minor RPS rated with ≥ 2 points each.

Test preparation, dose and mode of administration:

Double-blind treatment phase (day 1 - day 10):

Patients of the EPs® 7630 group received 30 drops orally three times a day.

Control preparation, dose and mode of administration:

Double-blind treatment phase (day 1 - day 10):

Patients of the placebo group received 30 drops orally three times a day.

Duration of treatment: Double-blind treatment period of ten days.

Criteria for evaluation:

Primary efficacy variable:

Area under the curve (AUC) of the total score of rhinopharyngitis-relevant symptoms (RPS) from baseline (day 1, visit 1) to day 5 (visit 3).

Secondary efficacy variables:

(1) Change in total score of rhinopharyngitis-relevant symptoms (RPS) from day 1 to day 3, from day 1 to day 5, and from day 1 to day 10, respectively, as assessed by the investigator

(2) Number of patients who experience a reduction in total score of RPS of at least 50% between baseline and day 5

(3) Number of patients with complete remission of RPS (total score of RPS = 0) or with substantial improvement of RPS (score of each symptom ≤ 1 point) as assessed by the investigator on day 3, 5, and 10, respectively

(4) Change in individual RPS from day 1 to day 3, from day 1 to day 5, and from day 1 to day 10, respectively, as assessed by the investigator

(5) Change in individual further rhinopharyngitis-relevant complaints from day 1 to day 3, from day 1 to day 5, and from day 1 to day 10, respectively, as assessed by the investigator

(6) Patient´s ability to work or to attend school/college as assessed by the patient in the patient´s diary

(7) Change in total score of general symptoms, as assessed by the patient in the patient´s diary

(8) Patient´s activity level as assessed by the patient in the patient´s diary

(9) Sleep quality as assessed by the patient in the patient´s diary

(10) Health-related Quality of Life (EQ-5D) as assessed by the patient on day 1, day 3, day 5, and day 10, respectively

(11) Time until onset of treatment effect as documented by the patient in the patient´s diary

(12) Treatment outcome according to the Integrative Medicine Outcomes Scale (IMOS) as assessed by the investigator as well as by the patient on day 3, day 5, and day 10, respectively

(13) Patient´s satisfaction with treatment according to the Integrative Medicine Patient Satisfaction Scale (IMPSS) as assessed by the patient on day 3, day 5, and day 10, respectively

(14) Consumption of paracetamol tablets

Safety:

- Adverse events surveillance
- Laboratory safety parameters

Statistical methods:

The confirmatory comparison of the treatment groups with respect to the primary outcome variable was conducted at a global one-sided type I error rate of α = 0.025 using an analysis of covariance with the factors treatment and centre and the baseline value of the RPS score as a covariate.

The current analysis was performed as an adaptive interim analysis (Bauer and Köhne, 1994) performed after completion of the treatment phase by 200 randomized patients. The following type I error rates and decision boundaries for the interim analysis were specified: Global one-sided type I error rate: α = 0.025; boundary for the one-sided p-value for accepting the null-hypothesis within the interim analysis: α_0 = 0.20; one-sided local type I error rate for testing the null-hypothesis within the interim analysis: α_1 = 0.0152; boundary for the product of one-sided p-values for the rejection of the null-hypothesis in the final analysis: c_α = 0.0038. The primary

analysis was based on the full analysis set (FAS). Methods of descriptive data analysis were applied for the evaluation of the secondary efficacy variables and the incidence of adverse events.

Results:

Demographic data

(absolute and relative frequency or mean ± standard deviation, respectively)

Full analysis set			
		Placebo (N=100)	**EPs® 7630 (N=101)**
Sex	Male	30 (30.0%)	37 (36.6%)
	Female	70 (70.0%)	64 (63.4%)
Age [y]		46.2±14.1	44.8±14.1
Weight [kg]		69.9±14.1	73.0±18.2
Height [cm]		167.8±8.8	168.8±9.6

Results of efficacy analysis:

Primary efficacy variable (AUC of the RPS total score between day 1 and day 5/day 10) (full analysis set)

(mean ± standard deviation

Full analysis set		
	Placebo (N=100)	**EPs® 7630 (N=101)**
AUC of RPS total score between day 1 and day 5	[redacted]	[redacted]
AUC of RPS total score between day 1 and day 10	[redacted]	[redacted]

Confirmatory analysis

Results of ANCOVA for AUC of the RPS total score (full analysis set)

(sample size, one-sided p-value of the ANCOVA with factors treatment group and centre and the baseline RPS total score as covariate; difference between estimated LS-means, one-sided 97.5% confidence interval for difference between LS-means; LOCF

Full analysis set (LOCF)			
	Number of observations used	**one-sided p-value ANCOVA***	**Difference of LS-means (EPs® 7630 - placebo) (One-sided 97.5%-CI)**
AUC of the RPS total score between day 1 and day 5	201	[redacted]	[redacted]
AUC of the RPS total score between day 1 and day 10	201	[redacted]	[redacted]

* for null-hypothesis: LS-mean (EPs® 7630) ≥ LS-mean (placebo)

Secondary efficacy variables: Total score of rhinopharyngitis-relevant symptoms (RPS) during the study and absolute changes from baseline (full analysis set)

(mean ± standard deviation; LOCF)

		Full analysis set	
		Placebo (N=100)	**EPs® 7630 (N=101)**
RPS total score	Baseline (day 1)	16.3±5.1	15.8±5.2
	Day 3	[redacted]	[redacted]
	Day 5	[redacted]	[redacted]
	Day 10	[redacted]	[redacted]
Change from baseline	Day 3	[redacted]	[redacted]
	Day 5	[redacted]	[redacted]
	Day 10	[redacted]	[redacted]

Secondary efficacy variables: Number of patients who experienced a reduction of the RPS total score of at least 50%, complete remission or substantial improvement (full analysis set)

(absolute and relative frequency; LOCF)

	Full analysis set	
	Placebo (N=100)	**EPs® 7630 (N=101)**
RPS total score - Improvement ≥ 50% at day 3	[redacted]	[redacted]
RPS total score - Improvement ≥ 50% at day 5	[redacted]	[redacted]
RPS total score - Improvement ≥ 50% at day 10	[redacted]	[redacted]
RPS total score - complete remission (total score = 0) at day 3	[redacted]	[redacted]
RPS total score - complete remission (total score = 0) at day 5	[redacted]	[redacted]
RPS total score - complete remission (total score = 0) at day 10	[redacted]	[redacted]
RPS total score - substantial improvement (score of each symptom ≤ 1) at day 3	[redacted]	[redacted]
RPS total score - substantial improvement (score of each symptom ≤ 1) at day 5	[redacted]	[redacted]
RPS total score - substantial improvement (score of each symptom ≤ 1) at day 10	[redacted]	[redacted]

Secondary efficacy variables: Changes in individual symptoms of the RPS total score

(mean ± standard deviation; LOCF)

		Full analysis set	
		Placebo (N=100)	**EPs® 7630 (N=101)**
Major symptom: Nasal discharge	Baseline (day 1)	2.4±0.6	2.4±0.6
	Day 5 - day 1	[redacted]	[redacted]
	Day 10 - day 1	[redacted]	[redacted]

		Full analysis set	
		Placebo (N=100)	**EPs® 7630 (N=101)**
Major symptom: Sore throat	Baseline (day 1)	2.2±0.6	2.4±0.7
	Day 5 - day 1	[redacted]	[redacted]
	Day 10 - day 1	[redacted]	[redacted]
Nasal congestion	Baseline (day 1)	2.4±0.7	2.3±0.6
	Day 5 - day 1	[redacted]	[redacted]
	Day 10 - day 1	[redacted]	[redacted]
Sneezing	Baseline (day 1)	1.4±0.9	1.4±0.9
	Day 5 - day 1	[redacted]	[redacted]
	Day 10 - day 1	[redacted]	[redacted]
Scratchy throat	Baseline (day 1)	2.0±0.8	2.0±0.8
	Day 5 - day 1	[redacted]	[redacted]
	Day 10 - day 1	[redacted]	[redacted]

Full analysis set			
		Placebo (N=100)	**EPs® 7630 (N=101)**
Hoarseness	Baseline (day 1)	1.3±1.0	1.2±0.9
	Day 5 - day 1	[redacted]	[redacted]
	Day 10 - day 1	[redacted]	[redacted]
Cough	Baseline (day 1)	1.3±0.9	1.4±1.0
	Day 5 - day 1	[redacted]	[redacted]
	Day 10 - day 1	[redacted]	[redacted]
Headache	Baseline (day 1)	1.5±0.9	1.4±0.8
	Day 5 - day 1	[redacted]	[redacted]
	Day 10 - day 1	[redacted]	[redacted]
Muscle aches	Baseline (day 1)	1.2±1.0	1.0±1.0
	Day 5 - day 1	[redacted]	[redacted]
	Day 10 - day 1	[redacted]	[redacted]
Fever	Baseline (day 1)	0.5±0.9	0.4±0.7
	Day 5 - day 1	[redacted]	[redacted]
	Day 10 - day 1	[redacted]	[redacted]

Secondary efficacy variables: Changes in further rhinopharyngitis-relevant complaints during the study (full analysis set)

(mean ± standard deviation; LOCF)

		Full analysis set	
		Placebo (N = 100)	**EPs® 7630 (N=101)**
Limb pain	Baseline (day 1)	0.8±1.0	0.8±1.0
	Day 5 - day 1	[redacted]	[redacted]
	Day 10 - day 1	[redacted]	[redacted]
Weakness all over	Baseline (day 1)	1.2±1.1	1.1±1.0
	Day 5 - day 1	[redacted]	[redacted]
	Day 10 - day 1	[redacted]	[redacted]
Exhaustion	Baseline (day 1)	0.9±1.1	0.9±1.0
	Day 5 - day 1	[redacted]	[redacted]
	Day 10 - day 1	[redacted]	[redacted]
Fatigue	Baseline (day 1)	1.0±1.0	1.0±1.0
	Day 5 - day 1	[redacted]	[redacted]
	Day 10 - day 1	[redacted]	[redacted]
Chilliness	Baseline	0.6±1.0	0.6±1.0
	Day 5 - day 1	[redacted]	[redacted]

	Full analysis set	
	Placebo (N = 100)	**EPs® 7630 (N=101)**
Day 10 - day 1	[redacted]	[redacted]

Secondary efficacy variables: Inability to work and physical activity level (day 10) (full analysis set)

(number of patients, mean ± standard deviation or absolute and relative frequency, respectively; LOCF)

		Full analysis set	
		Placebo (N = 100)	**EPs® 7630 (N=101)**
Number of days of inability to work		98 [redacted]	100 [redacted]
Physical activity level at day 10	100% of usual level	[redacted]	[redacted]
	75% of usual level	[redacted]	[redacted]
	50% of usual level	[redacted]	[redacted]
	25% of usual level	[redacted]	[redacted]
	0% of usual level	[redacted]	[redacted]
	Missing	[redacted]	[redacted]

Secondary efficacy variables: Sleep quality and quality of life (EQ-5D)

(full analysis set)

(number of patients, mean ± standard deviation; LOCF)

		Full analysis set	
		Placebo (N = 100)	**EPs® 7630 (N=101)**
Sleep Quality	Day 1	75 [redacted]	82 [redacted]
	Day 10 - day 1	75 [redacted]	82 [redacted]
Quality of Life (EQ-5D) Total Score	Day 1	98 [redacted]	101 [redacted]
	Day 10 - day 1	97 [redacted]	101 [redacted]
Quality of Life (EQ-5D) VAS	Day 1	99 [redacted]	101 [redacted]
	Day 10 - day 1	98 [redacted]	101 [redacted]

Secondary efficacy variables: Time until onset of treatment effect (full analysis set)

(absolute and relative frequency; LOCF)

Full analysis set			
		Placebo (N = 99)	**EPs® 7630 (N=97)**
Time until onset of treatment effect [days]	≤ 1 day	[redacted]	[redacted]
	2-3 days	[redacted]	[redacted]
	4-6 days	[redacted]	[redacted]
	7-10 days	[redacted]	[redacted]
	not at all	[redacted]	[redacted]

Secondary efficacy variables: Integrative Medicine Outcome Scale (IMOS) at day 10 - investigator and patient assessment (full analysis set)

(absolute and relative frequency; LOCF)

Full analysis set			
		Placebo (N = 100)	**EPs® 7630 (N=101)**
Integrative Medicine Outcome Scale (IMOS) - Investigator assessment	Complete recovery	[redacted]	[redacted]
	Major improvement	[redacted]	[redacted]
	Slight to moderate improvement	[redacted]	[redacted]
	No change	[redacted]	[redacted]
	Deterioration	[redacted]	[redacted]
		Placebo (N = 99)	**EPs® 7630 (N=101)**
Integrative Medicine Outcome Scale (IMOS) - Patient assessment	Complete recovery	[redacted]	[redacted]
	Major improvement	[redacted]	[redacted]
	Slight to moderate improvement	[redacted]	[redacted]
	No change	[redacted]	[redacted]
	Deterioration	[redacted]	[redacted]

Secondary efficacy variables: Integrative Medicine Patient Satisfaction Scale (IMPSS) at day 10 (full analysis set)

(absolute and relative frequency; LOCF)

Full analysis set			
		Placebo (N = 99)	**EPs® 7630 (N=101)**
Integrative Medicine Patient Satisfaction Scale (IMPSS)	Very satisfied	[redacted]	[redacted]
	Satisfied	[redacted]	[redacted]
	Neutral	[redacted]	[redacted]
	Dissatisfied	[redacted]	[redacted]
	Very dissatisfied	[redacted]	[redacted]

Secondary efficacy variables: Consumption of paracetamol tablets

Throughout the study [redacted] patients in the [redacted] group than in the [redacted] group used paracetamol: between day 1 and day 3 there were [redacted] patients in the [redacted] treatment group compared to [redacted] patients in the [redacted] treatment group, between day 3 and day 5 there were [redacted] patients in the [redacted] treatment group compared to [redacted] patients in the [redacted] treatment group, and between day 5 and day 10 there was [redacted] patient in the [redacted] treatment group compared to [redacted] patients in the [redacted] treatment group who took paracetamol (full analysis set) .

Results of safety analysis

Patients with adverse events (safety analysis set):

Double-blind treatment period	EPs® 7630	[redacted] patients ([redacted]%)	([redacted] adverse events)
	Placebo	[redacted] patients ([redacted]%)	([redacted] adverse events)

Patients with serious adverse events:

No death or other serious adverse events occurred during the course of the study.

Conclusion

This multicentre, randomized, double-blind, placebo-controlled parallel-group study was conducted to evaluate the efficacy and tolerability of EPs® 7630 in patients (≥18 years old) with acute rhinopharyngitis (ARP). During the ten days of treatment patients received 30 drops three times a day of EPs® 7630 solution or placebo solution.

The primary efficacy analysis was based on the FAS including all patients having received randomized study medication at least once and having at least one efficacy measurement during active treatment period.

In the safety analysis, a total of 201 randomized patients (EPs® 7630 solution: 101 patients, placebo: 100 patients) could be evaluated. All of these patients contributed efficacy data at least at day 3 and thus were also included in the FAS.

In summary, in this study with the applied trial setting the null-hypothesis could [redacted]. However, the trial had several limitations. First, there are no validated instruments for assessing the symptoms of acute rhinopharyngitis. Therefore the primary efficacy variable of the study – with exception of fever severity - is based on subjective symptoms severity assessment made by the patients that can introduce several potential biases (Mossad, 2003; Barrett et al., 2002). Second, no objective measure of an acute rhinopharyngitis, i.e. microbiological diagnosis, was carried out at baseline prior to patients´ inclusion into the study that, however, is justified by the fact that this is not routinely carried out in the daily practice; the diagnosis was relied solely on patients´ subjective information. Third, as it is thought that the therapy with EPs® 7630 should be initiated as early as possible and at the first signs of an acute rhinopharyngitis to be effective, it is conceivable that both the allowed time window for having the symptoms of the study indication (up to 3 days) before inclusion into the study as well as the number of symptoms (4 symptoms) and their severity score of at least 8 points in total that had to be present at the time point of inclusion may have resulted in the present study outcome. In other common cold trials with results showing superiority over placebo using other products, treatment was begun contemporarily when patients had a first subjective feeling of cold (Schulten et al., 2001; Prassad et al., 2000; Hoheisel et al., 1997; Mossad et al., 1996). However, neither the time point of treatment start nor the number or severity of the symptoms present at study entry seem to represent a determinant factor for a study outcome showing superiority over placebo as the

same products used in the above mentioned trials failed to show beneficial effects on common cold symptoms when tested by other investigators using comparable trial settings (Barrett et al., 2010, 2002; Eby and Halcomb, 2006; Macknin et al., 1998). Finally, even though the enrolled patients were instructed not to use symptom relief medication with the exception of paracetamol, covert use of other cold remedies cannot be certainly excluded. Although common cold is a self-limiting illness in otherwise healthy persons, the spontaneous symptom improvements in the placebo group with nearly [redacted] of the patients improved at least by 50% until day 5 in the present study, however, were very high. Concerning safety the study clearly shows that EPs® 7630 is very well tolerated. This is in accordance with the existing safety data, which is further supported by the results presented in this report.