SUMMARY OF RESULTS

Safety and tolerability of Pelargonium sidoides extract EPs® 7630 in children (1 to 5 years old) suffering from acute bronchitis

A prospective, multi-centre, randomised safety study

Results of the final analysis

Study No. 701003.01.010

Eudra-CT-No.: 2011-002652-14

Date of report: 14 September 2018

First subject included: 28 November 2011

Last subject completed: 21 December 2012

Completion of study (defined as clean data): 25 March 2013

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SUMMARY

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

Study title: Safety and tolerability of Pelargonium sidoides extract EPs® 7630 in children (1 to 5 years old) suffering from acute bronchitis.

Relevant amendments: None

Co-ordinating Investigator according to ICH-GCP: The study was conducted by one co-ordinating investigator in Germany.

Investigators: The study was conducted by 34 investigators in Germany.

Study centres: The study was conducted in 35 study centres in Germany.

Study period: First subject included: 28 November 2011
Last subject completed: 21 December 2012

Publications: None

Clinical phase: IV

Objectives:

Primary objective:

The primary objective of the clinical trial was to evaluate the safety and tolerability of a treatment with EPs® 7630 syrup in comparison to EPs® 7630 solution in patients between 1 and 5 years old suffering from acute bronchitis.

Secondary objectives:

During the study course the patients' health status was also assessed.

Methodology: The clinical trial was conducted as a prospective, randomised, multi-centre safety study in Germany.

Number of subjects included in the analysis:

Treatment group	Planned to be randomised	Randomised	Patients taken into account for the analysis		
			Safety	Efficacy	
			Safety set	Full analysis set	Per protocol set
EPs® 7630 syrup	400	411	403	403	370
EPs® 7630 solution	200	191	188	188	155
All	600	602	591	591	525

Diagnosis and main criteria for inclusion: Patients included were children from 1 year to 5 years old and suffering from symptoms related to acute bronchitis: the patients were required to present at least two of the three bronchitis-relevant symptoms, i.e. coughing, pulmonary rales at auscultation, and dyspnoea. For all patients included, the legal representatives had to give written informed consent in accordance with the legal requirements. The start of symptoms was ≤ 72 hours prior to inclusion into the study.

Test preparations, dose and mode of administration: EPs® 7630 syrup and EPs® 7630 solution, respectively, was applied orally in the following doses:

EPs® 7630 syrup: 2.5 ml three times daily for 7 days

EPs® 7630 solution: 10 drops three times daily for 7 days

Control preparation, dose and mode of administration: Not applicable

Duration of treatment: The investigational product was to be taken during the whole individual treatment period of the clinical trial (7 consecutive days).

Criteria for evaluation: **Safety / tolerability**:

- Frequency, severity and nature of adverse events
- Changes in vital signs
- Changes in laboratory values.

Patient's health status:

- Changes in individual respiratory tract infection symptoms related to acute bronchitis as well as the total symptoms score
- Treatment outcome using the Integrative Medicine Outcomes Score (IMOS) as assessed by the investigator as well as by the legal representatives of the patients
- Satisfaction with the treatment using the Integrative Medicine Patient Satisfaction Scale (IMPSS) as assessed by the legal representatives of the patients.

Statistical methods: The primary aim of the study was to obtain information about the safety of a 7-day treatment with the EPs® 7630 syrup in comparison to the EPs® 7630 solution in children between 1 and 5 years of age suffering from acute respiratory tract infection symptoms related to acute bronchitis. Since this study was a randomised open-label safety study no hypothesis was formulated and the data were analysed in an exploratory way.
Accordingly, all two-sided p-values resulting from any statistical test or model are to be interpreted in a descriptive manner.

Due to the design of the study there was no formal estimation of sample size accounting for type I error rate, power, standard deviation, and effect size.
For continuous data, the basic statistics, e.g. sample size, number of missing values, mean and standard deviation were

calculated together with the 95% confidence interval (CI) for the mean.

Categorical data were displayed in frequency tables showing sample size, absolute and relative frequency. Percentages were generally quoted using the number of available values in the denominator.

The safety analysis included a descriptive comparison of the treatment groups regarding the incidence, type, and severity of AEs.

Laboratory data (ALT, AST, Gamma-GT and CRP) were summarised by means of descriptive statistics, including 95% confidence intervals for the mean - for both, Baseline (Day 0, visit 1) and Day 7 (study end, visit 2) as well as the differences between these visits.

For further comparisons between the safety profiles of EPs® 7630 solution and syrup, historical data from three other available studies with EPs® 7630 solution in children with acute bronchitis were considered. An integrated analysis of all AEs and suspected AEs of the historical data and the current study assigned to the 4 system groups (gastrointestinal complaints, hypersensitivity reactions, nasal and gingival bleeding, as well as liver associated events), listed in the SmPCs of the marketed products, was performed: estimation of AEs and suspected AEs including the appropriate 95% confidence intervals; calculation of risk differences with their 95% confidence intervals as well as the two-sided chi-squared test for risk differences between EPs® 7630 solution and syrup.

Results:

Demographic data: all patients (safety analysis set / full analysis set)

(number (percentage) of patients and p-value of the two-sided χ^2-test or mean ± standard deviation and p-value of the two-sided t-test, respectively)

Parameter		EPs® 7630 syrup N=403	EPs® 7630 solution N=188	Total N=591	p-value
Sex	Male	214 (53.1%)	102 (54.3%)	316 (53.5%)	0.793
	Female	189 (46.9%)	86 (45.7%)	275 (46.5%)	
Age [y]		3.03±1.33	2.96±1.39	3.01±1.35	0.545
Height [cm]		99.1±11.7	99.0±12.3	99.1±11.9	0.971
Weight [kg]		15.8±3.9	15.9±3.9	15.8±3.9	0.823

Results of patient's health status:

Change in the individual symptoms of the Bronchitis Severity Scale (BSS) and total score (Day 7 – Baseline, full analysis set)

(mean ± standard deviation [95% confidence intervals]; LOCF)

BSS-Symptom	EPs® 7630 syrup N=403	EPs® 7630 solution N=188	Total N=591
Coughing*	[redacted]	[redacted]	[redacted]
Pulmonary rales at auscultation	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Total Score	[redacted]	[redacted]	[redacted]

* during the last 24 hours preceding the time point of visit 2

Change in the individual symptoms of the BSS (Day 7 – Baseline, full analysis set)
(number (percentage) of patients, LOCF)

BSS-Symptom	EPs® 7630 syrup N=403	EPs® 7630 solution N=188	Total N=591
Coughing			
Remission	[redacted]	[redacted]	[redacted]
Improvement	[redacted]	[redacted]	[redacted]
No change	[redacted]	[redacted]	[redacted]
Deterioration	[redacted]	[redacted]	[redacted]
Pulmonary rales at auscultation*	N=395	N=186	N=581
Remission	[redacted]	[redacted]	[redacted]
Improvement	[redacted]	[redacted]	[redacted]
No change	[redacted]	[redacted]	[redacted]
Deterioration	[redacted]	[redacted]	[redacted]
Dyspnoea*	N=201	N=82	N=283
Remission	[redacted]	[redacted]	[redacted]
Improvement	[redacted]	[redacted]	[redacted]
No change	[redacted]	[redacted]	[redacted]
Deterioration	[redacted]	[redacted]	[redacted]

*Number of patients with symptom on Day 0, calculation of rates is based on these baseline numbers.
Remission: Symptom mild, moderate, severe or very severe on Day 0 and not present on Day 7.
Improvement: Any decrease in symptom intensity from Day 0 to Day 7 except remission.
No change: No change in symptom intensity from Day 0 to Day 7.
Deterioration: Any increase in symptom intensity from Day 0 to Day 7.

Therapy outcome using the integrative medicine outcomes scale (IMOS) at Day 7 (full analysis set)
(number (percentage) of patients)

Parameter		EPs® 7630 syrup N=403	EPs® 7630 solution N=188
Therapy outcome (assessed by investigator)	Complete recovery	[redacted]	[redacted]
	Major improvement	[redacted]	[redacted]
	Slight to moderate improvement	[redacted]	[redacted]
	No change	[redacted]	[redacted]
	Deterioration	[redacted]	[redacted]
	Missing	[redacted]	[redacted]
Therapy outcome (assessed by legal representative)	Complete recovery	[redacted]	[redacted]
	Major improvement	[redacted]	[redacted]
	Slight to moderate improvement	[redacted]	[redacted]
	No change	[redacted]	[redacted]
	Deterioration	[redacted]	[redacted]
	Missing	[redacted]	[redacted]

Patient's satisfaction with treatment using the integrative medicine patient satisfaction scale (IMPSS) at Day 7 (full analysis set)
(number (percentage) of patients)

Parameter		EPs® 7630 syrup N=403	EPs® 7630 solution N=188
Therapy satisfaction (assessed by legal representative)	Very satisfied	[redacted]	[redacted]
	Satisfied	[redacted]	[redacted]
	Neutral	[redacted]	[redacted]
	Dissatisfied	[redacted]	[redacted]
	Very dissatisfied	[redacted]	[redacted]
	missing	[redacted]	[redacted]

Results of safety analysis

Number and incidence of adverse events (safety analysis set)
(EPs® 7630 syrup – all patients, N = 403)

Study period	Patients in study	Patients with adverse events	Observation days	Number of adverse events	Events per observation day
Active treatment phase	403	[redacted]	[redacted]	[redacted]	[redacted]
7 days risk phase	403	[redacted]	[redacted]	[redacted]	[redacted]
Active treatment or risk phase	403	[redacted]	[redacted]	[redacted]	[redacted]

Number and incidence of adverse events (safety analysis set)
EPs® 7630 solution – all patients, N = 188)

Study period	Patients in study	Patients with adverse events	Observation days	Number of adverse events	Events per observation day
Active treatment phase	188	[redacted]	[redacted]	[redacted]	[redacted]
7 days risk phase	188	[redacted]	[redacted]	[redacted]	[redacted]
Active treatment or risk phase	188	[redacted]	[redacted]	[redacted]	[redacted]

Patients with adverse events (safety analysis set):

Study phase	Treatment group	Number of patients (absolute (relative))	Number of adverse events
Treatment phase and risk phase	EPs® 7630 syrup	[redacted]	[redacted]
	EPs® 7630 solution	[redacted]	[redacted]

Patients with serious adverse events:

[redacted] occurred in [redacted] which [redacted] assessed as "[redacted]" to the investigational product. [redacted].

Number of patients with adverse events (MedDRA preferred terms) that occurred in more than three patients in one group (safety analysis set)

(number (percentage) of patients)

Preferred term	EPs® 7630 syrup N=403		EPs® 7630 solution N=188	
Vomiting*	[redacted]		[redacted]	
Otitis media				

*Vomiting was reported at Baseline in 37/403 (9.2%) patients and in 14/188 (7.5%) patients in the syrup group and the solution group, respectively.

Patients with adverse events, for which a causal relationship to the investigational product could not be excluded (safety analysis set)

Study phase	Treatment group	Number of patients (absolute (relative))	Number of ADRs
Treatment phase and risk phase	EPs® 7630 syrup	[redacted]	[redacted]
	EPs® 7630 solution	[redacted]	[redacted]

Liver enzymes and CRP: Mean changes Day 7 – Baseline (safety analysis set)
(N, mean ± standard deviation [95% confidence intervals])

Laboratory parameter	EPs® 7630 syrup	EPs® 7630 solution
ALT (U/l)	N = 380 [redacted]	N = 178 [redacted]
AST (U/l)	N = 379 [redacted]	N = 179 [redacted]
Gamma-GT (U/l)	N = 379 [redacted]	N = 179 [redacted]
CRP (mg/l)	N = 381 [redacted]	N = 176 [redacted]

Integrated analysis of patients with adverse events from historical data (3 studies with EPs® 7630 solution) and the current study assigned to the 4 system organ groups (gastrointestinal complaints, hypersensitivity reactions, nasal and gingival bleeding, and liver associated events), listed in the SmPCs of the marketed products (safety analysis set – children 1-5 years old)

(number (percentage) of patients [95% confidence interval], two-sided p-value of χ^2-tests)

System group	EPs® 7630 syrup N=403	EPs® 7630 solution N=456	Risk difference	p-value
Gastrointestinal complaints	13 (3.23%) [1.89%;5.44%]	19 (4.17%) [2.68%;6.42%]	-0.94% [-3.55%;1.72%]	0.467
Hypersensitivity reactions	[redacted]	[redacted]	[redacted]	[redacted]
Nasal and gingival bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Liver associated events	[redacted]	[redacted]	[redacted]	[redacted]

CONCLUSION

The objective of this randomised, open-label, multi-centre clinical study was to evaluate the safety and tolerability of a 7-day treatment with EPs® 7630 syrup in comparison to EPs® 7630 solution in children between 1 and 5 years old suffering from acute respiratory tract infection symptoms related to acute bronchitis. Additionally, the patients´ health status was assessed during the course of the study. The primary outcome variables as to safety were the frequency, severity and nature of adverse events, changes in vital signs and in laboratory parameters with the focus on liver enzymes (ALT, AST, Gamma-GT) as well as C-reactive protein (CRP). The outcome variables with respect to the patient's health status were changes in the severity of individual and total bronchitis-specific symptoms as well as other respiratory tract infection symptoms related to acute bronchitis, the treatment outcome using the Integrative Medicine Outcomes Score (IMOS) and satisfaction with the treatment using the Integrative Medicine Patient Satisfaction Scale (IMPSS).

As this study was an open-label safety study, no hypotheses were formulated and the data were analysed in an exploratory way. Accordingly, all two-sided p-values resulting from any statistical test or model are to be interpreted descriptively..

A total of 602 patients (aged 1 to 5 years) were screened for inclusion into this safety study which was performed in 35 centres in Germany. All 602 patients were randomised in a ratio of 2:1, 411 of them to receive EPs® 7630 syrup and 191 to receive EPs® 7630 solution. Eleven children (EPs® 7630 syrup: 8 / EPs® 7630 solution: 3) were drop-outs without any intake of the investigational product. The remaining 591 patients received the investigational product at least once (EPs® 7630 syrup: 403 patients, EPs® 7630 solution: 188 patients) and were included in the safety analysis set (SAF) which corresponds to the full analysis set (FAS). Relevant protocol violations were observed in 66 patients and hence a total of 525 patients were included in the per protocol set (PPS; EPs® 7630 syrup: 370 patients, EPs® 7630 solution: 155 patients). Since the analyses of the FAS and the PPS revealed similar results, the evaluation of the FAS is shown in this report.

At Baseline, demographic data like age, weight and height of patients as well as the total score of bronchitis-specific symptoms and further bronchitis associated respiratory tract infection symptoms including vomiting as well as the Integrative Medicine Outcome Scale were comparable between both treatment groups. The mean treatment duration of all patients was [redacted] days and was [redacted] (EPs® 7630 syrup: [redacted]; EPs® 7630 solution: [redacted]).

Regarding the analysis of the patients' health status, the [redacted] in the total score of bronchitis-specific symptoms (i.e. coughing, pulmonary rales at auscultation and dyspnoea) from Day 0 to Day 7 were [redacted] in [redacted]. The remission and improvement rates of individual bronchitis-specific symptoms from Baseline to Day 7 were more than [redacted] for each symptom and [redacted] as well. Average improvements were also observed for all other bronchitis-associated symptoms assessed. Especially the number of children reporting [redacted] at Day 7 was [redacted] in [redacted] as compared to Baseline. According to the general health status (IMOS), more than [redacted] of the patients in both EPs®-7630-treatment-groups had completely recovered or showed a major improvement at Day 7 as assessed by the investigators as well as by the legal representatives. According to the Integrative Medicine Patient Satisfaction Scale (IMPSS), the legal representatives of the patients were '*very satisfied'* or '*satisfied'* with the treatment in more than [redacted] of patients during the therapy.

The safety evaluation showed that the number of adverse events (AEs) during the study (active treatment period and a 7 days risk phase) was low and comparable between both EPs®-7630-treatment-groups. The causality of most AEs was assessed as '[redacted]' to the investigational product. Only in very few cases (EPs® 7630 syrup: [redacted] adverse drug reactions (ADR), EPs® 7630 solution: [redacted] ADRs), a causal relationship with the study drug could not be excluded, but was assessed as '[redacted]' in all cases, except [redacted] with the assessment '[redacted]'. This resulted in a very low incidence of ADRs of [redacted] and [redacted] per observation day for EPs® 7630 syrup and EPs® 7630 solution treated patients, respectively. The distribution of adverse events according to the System Organ Classes (SOC) was [redacted] with [redacted] in [redacted]. The SOC with the largest number of patients affected by adverse events was the SOC '[redacted]' followed by '[redacted]'. Most AEs were of [redacted] intensity. Only [redacted] occurred during the study – the causality of [redacted] assessed as [redacted] the investigational product. Laboratory analysis of liver enzymes ALT, AST and Gamma-GT showed [redacted] on average between Day 7 and Baseline. Individual analyses of liver enzyme values revealed that in most cases [redacted] of EPs® 7630 syrup and [redacted] of EPs® 7630 solution patients showed [redacted] at Day 7 which were reported as adverse events (EPs® 7630 syrup: [redacted]: [redacted], [redacted]: [redacted]; EPs® 7630 solution: [redacted]: [redacted], [redacted]: [redacted]). [redacted] of these patients did [redacted] from [redacted] and [redacted] at treatment end. [redacted] with [redacted] at Day 7 already had [redacted]

[redacted] at Baseline. In [redacted] of the children the elevated liver values expressed any clinical symptoms. Thus the relationship with the investigational product can be assessed as [redacted]. A multicentre prospective study in children with an acute respiratory infection showed an increase of liver enzymes in 8.3% of patients (Stein et al., 2010). With an overall rate of [redacted] patients with liver-associated AEs in both EPs®-7630-treatment-groups - all due to [redacted] - this rate is [redacted] than the corresponding frequency within the general population (8-11%), especially as those elevations are correlated with respiratory infections (Berg, 2009).

An integrated analysis of adverse events from historical data of three studies in children with acute bronchitis (Kamin et al. 2010, Kamin et al. 2012 and Matthys et al. 2007) and the current study assigned to the 4 terms (gastrointestinal complaints, hypersensitivity reactions, nasal and gingival bleeding, and liver associated events) listed in the SmPCs of the marketed products was performed. [redacted] in the number of AEs or ADRs between the two application forms could be observed, [redacted] in the current study [redacted] in the integrated analysis of the pooled data.

In summary, the study proves the safety and tolerability of both application forms of EPs® 7630 in infants. Assessments evaluating patient's health and patient's satisfaction with treatment were [redacted] in [redacted]. The number of AEs was [redacted] and [redacted] with a [redacted] of ADRs. The laboratory analysis of liver enzymes ALT, AST, and Gamma-GT showed [redacted] between Day 7 and Baseline in either group. The results suggest that both application forms of EPs® 7630, the solution as well as the syrup, are safe and well-tolerated medicinal products for the treatment of acute bronchitis in children between 1 and 5 years of age.

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