# Summary of results

# Version 1.0

## Safety and intake effect of EPs® 7630 (an extract of the roots of *Pelargonium sidoides*): a prospective, monocentric, randomised, double-blind, placebo-controlled clinical trial

**Clinical trial No. 701079.01.013**

EudraCT No. 2013-004977-28

Date of report: 07 September 2017

First subject included: 27 March 2014

Last subject completed: 24 July 2015

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# 1 SUMMARY

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

**Title of clinical trial:** Safety and intake effect of EPs® 7630 (an extract of the roots of Pelargonium sidoides): a prospective, monocentric, randomised, double-blind, placebo-controlled clinical trial

**Relevant Amendments:** Not applicable

**Scientific Advisor:** One scientific advisor in the United Kingdom.

**Principal investigator** One principal investigator in the United Kingdom.

**Investigator:** As above

**Trial sites:** The study was conducted in one study centre in the United Kingdom.

**Trial period:** First subject included: 27 March 2014

Last subject completed: 24 July 2015

**Publications:** Not applicable

**Clinical phase:** Phase III

**Objective:**

**Primary objective**

The primary objective was to investigate the occurrence of adverse drug reactions (ADRs) during the 4 months treatment, defined as the proportion of participants in each trial group with suspected adverse events.

**Secondary objectives**

A) Occurrence of adverse events (AEs) during the 4 months treatment:
   1- Number of ADRs in each trial group
   2- Proportion of participants with AEs in each trial group
   3- Number of AEs in each trial group

B) Protective effects:

1- Time to onset of first common cold symptoms during the trial in each trial group
2- Time between last common cold episode prior to trial entry and first cold episode during the trial
3- Total number of common cold episodes during the trial in each trial group
4- Total number of participants with at least one common cold episode during the trial in each trial group
5- Total number of participants with more than one common cold episode during the trial in each trial group

C) Effects during a cold episode:

1- Mean cold episode duration (in days) in each trial group
2- Cumulative episode days in each trial group
3- Number of co-medicated cold episodes in each trial group
4- Number of participants with respiratory complications (e.g. otitis media, sinusitis, lower respiratory tract infection (LRTI)) due to common cold
5- Development of the total cold symptom score during a cold episode
6- Development of individual symptoms during a cold episode

**Methodology**:

Prospective, monocentric, randomised, double-blind, placebo-controlled trial with 2 parallel treatment groups (active medication and placebo). The trial was planned for an inclusion of 720 subjects - 480 subjects treated with EPs® 7630 film-coated tablets (Group 1) and 240 subjects treated with placebo (Group 2).

The individual duration of the clinical trial was 4 months starting from day 0 (baseline) to month 4 (final visit). During this time 5 visits were scheduled: visit 1 (on day 1), visit 2 (1 month ± 2 days after randomisation), visit 3 (2 months ± 2 days after randomisation), visit 4 (3 months ± 2 days after randomisation), and visit 5 (4 months ± 2 days after randomisation).

**Number of subjects included in the analysis**

| | | EPs® 7630 | | | |
|---|---|---|---|---|---|
| | Placebo | 3x20 mg | 3x20/40 mg* | Overall | Overall |
| | (N=239) | (N=240) | (N=241) | (N=481) | (N=720) |
| Set | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Included** | | | | | |
| **Randomised** | | | | | |
| **Safety set (SAF)** | 223 (93.3) | 230 (95.8) | 230 (95.4) | 460 (95.6) | 683 (94.9) |
| **Full analysis set (FAS)** | 222 (92.9) | 229 (95.4) | 227 (94.2) | 456 (94.8) | 678 (94.2) |

* 3x20/40 mg: trial group who was randomised to 3x20 mg/day during common cold free periods and 3x40 mg/day during common cold periods

**Diagnosis and main criteria for inclusion:**

1. Adult male or female subject (≥ 18 years old)
2. Subject provided a written informed consent in accordance with the legal requirements
3. Subject with willingness and ability to comply with all procedures of the clinical trial and be available for the duration of the trial
4. Subject is of good physical and mental condition
5. Subject experienced ≥ 2 colds per year in the last 12 months

**Test preparation, dose mode of administration:**

EPs® 7630 film-coated tablets (FCT) containing 20 mg of dried EPs® 7630

**Medication I: common cold free period (Box I)**

Group 1: one tablet (20 mg) 3 times daily orally

**Medication II: during a common cold period (for 14 consecutive days) (Box II)**

Active medication Group 1 is divided into two subgroups:

- Subgroup A: active medication I:

  On the day the participant believes to have a cold and documents this in the diary accordingly, he/she ingests two film-coated tablets (1 x 20 mg and 1 x placebo) three times a day (in the morning, midday and evening; total daily dose 60 mg) over the individual treatment duration of 14 consecutive days, or

- Subgroup B: active medication II (high dose):

  On the day the participant believes to have a cold and documents this in the diary accordingly, he/she ingests two

film-coated tablets (2 x 20 mg = 40 mg) three times a day (in the morning, midday and evening; total daily dose 120 mg) over the individual treatment duration of 14 consecutive days.

**Control preparation, dose and mode of administration:**

Placebo

**Medication I: common cold free period (Box I)**

Group 2: one tablet 3 times daily orally

**Medication II: during a common cold period (for 14 consecutive days) (Box II)**

Group 2: 3 x 2 FCTs/day orally (2 x placebo FCTs)

**Duration of treatment:** 4 consecutive months

**Criteria for evaluation**

**Safety:**

Primary outcome criterion:

Occurrence of adverse drug reactions (ADRs) during the 4 months treatment, defined as the proportion of participants in each trial group with suspected adverse events

Secondary outcome criteria:

- Number of ADRs in each trial group
- Proportion of participants with AEs in each trial group
- Number of AEs in each trial group

Routine blood laboratory testing

Vital signs

**Intake effect:**

Protective effects throughout assessing:

- Time to onset of first common cold symptoms during the trial in each trial group
- Time between last common cold episode prior to trial entry and first cold episode during the trial
- Total number of common cold episodes during the trial in each trial group
- Total number of subjects with at least one common cold episode during the trial in each trial group
- Total number of subjects with more than one common cold episode during the trial in each trial group

Effects during a cold episode throughout assessing:

- Mean cold episode duration (in days) in each trial group
- Cumulative episode days in each trial group
- Number of co-medicated cold episodes in each trial group
- Number of patients with respiratory complications (e.g. otitis media, sinusitis, LRTI) due to common cold
- Development of the total cold symptom score during a cold episode
- Development of individual symptoms during a cold episode

**Other measures:**

- Integrative Medicine Patient Satisfaction Scale (IMPSS)
- Subject's diary

**Statistical methods:**

The primary aim of this trial was to obtain further information about the safety and tolerability of EPs® 7630 film-coated tablets - used as continuous prophylaxis and at the onset of cold symptoms - in adult subjects.

The trial was designed as a randomised, double-blind and placebo-controlled trial. Due to the sparseness of empirical data in the population and this setting, no confirmatory hypotheses were formulated and the data were analysed descriptively, which is in line with the ICH E9 guideline.

Sample size calculation was based on the assumption that a prophylactic intake of EPs® 7630 tablets does not increase the risk beyond a clinically unacceptable size (non-inferiority or safety margin) in comparison to placebo. Assumptions were:

- a proportion of participants with ADRs within the EPs® 7630 total and placebo group of 0.2
- a margin of 10%
- a one-sided type I error rate of 2.5%
- a power of 80%

Descriptive statistics were supplied according to the nature of the criteria:

- Quantitative variable: sample size, arithmetic mean and 95% confidence interval (CI), standard deviation (SD), standard error of the mean (SEM), minimum, median, and maximum, quartiles
- Qualitative variable: sample size, absolute and relative frequencies per class. Percentages were provided with one decimal place.

Data were organized by treatment group:

- EPs® 7630 3x20 mg
- EPs® 7630 3x20/40 mg
- EPs® 7630 – Overall
- Placebo

All listings were sorted by treatment group, subject and measurement time if applicable (e.g. visit or date in case of diary entries) and included in the analysis sets.

For all parameters, baseline was defined as the last available measurement prior to the first IMP administration.

Unless otherwise stated, statistical tests were two-sided and were carried out at the 5% level of significance.

**RESULTS:**

**Demographic Data**

The mean age±SD of the trial population in the SAF was 21.5±6.1 years, 21.0±5.0 in the placebo and 21.7±6.6 in the EPs® 7630 population, a large majority of subjects (642, 94.0%) was Caucasian. Almost twice as many female (439, 64.3%) as male (244, 35.7%) subjects participated in the trial, data were similar for both treatment groups. Results are based on the SAF.

**Demographic data and other factors potentially affecting response (SAF)**

| Parameter (unit) | Statistics / Category | Placebo (N=223) | EPs® 7630 3x20 mg (N=230) | EPs® 7630 3x20/40 mg (N=230) | EPs® 7630 Overall (N=460) | Overall (N=683) |
|---|---|---|---|---|---|---|
| Age (years) | n | 223 | 230 | 230 | 460 | 683 |
| | Mean ± SD | 21.0 ± 5.0 | 21.6 ± 6.5 | 21.9 ± 6.7 | 21.7 ± 6.6 | 21.5 ± 6.1 |
| | **p-value*** | | | **0.1240** | | |
| Gender | Female (n,%) | 148 (66.4) | 151 (65.7) | 140 (60.9) | 291 (63.3) | 439 (64.3) |
| | Male (n,%) | 75 (33.6) | 79 (34.3) | 90 (39.1) | 169 (36.7) | 244 (35.7) |
| | **p-value*** | | | **0.4269** | | |
| Ethnic origin | White/Caucasian (n,%) | 210 (94.2) | 221 (96.1) | 211 (91.7) | 432 (93.9) | 642 (94.0) |
| | Black (n,%) | 4 ( 1.8) | 1 ( 0.4) | 3 ( 1.3) | 4 ( 0.9) | 8 ( 1.2) |
| | Asian (n,%) | 9 ( 4.0) | 7 ( 3.0) | 13 ( 5.7) | 20 ( 4.3) | 29 ( 4.2) |
| | Other (n,%) | 0 ( 0.0) | 1 ( 0.4) | 3 ( 1.3) | 4 ( 0.9) | 4 ( 0.6) |
| | **p-value*** | | | **0.3810** | | |
| Height (cm) | n | 223 | 230 | 230 | 460 | 683 |
| | Mean ± SD | 168.9 ± 8.1 | 169.2 ± 8.7 | 170.4 ± 9.0 | 169.8 ± 8.8 | 169.5 ± 8.6 |
| | **p-value*** | | | **0.2212** | | |
| Weight (kg) | n | 223 | 230 | 230 | 460 | 683 |
| | Mean ± SD | 68.2 ± 10.9 | 67.7 ± 12.0 | 70.1 ± 13.3 | 68.9 ± 12.8 | 68.7 ± 12.2 |
| | **p-value*** | | | **0.4941** | | |
| BMI (kg/m²) | n | 223 | 230 | 230 | 460 | 683 |
| | Mean ± SD | 23.87 ± 3.32 | 23.58 ± 3.37 | 24.01 ± 3.57 | 23.79 ± 3.47 | 23.82 ± 3.42 |
| | **p-value*** | | | **0.7649** | | |

* Characteristics are compared between overall EPs® 7630 group and Placebo group using the t-test for quantitative variables and the chi-square test for qualitative variables.

**Demographic data and other factors potentially affecting response (FAS)**

| Parameter (unit) | Statistics / Category | Placebo (N=222) | EPs® 7630 3x20mg (N=229) | EPs® 7630 3x20/40mg (N=227) | EPs® 7630 Overall (N=456) | Overall (N=678) |
|---|---|---|---|---|---|---|
| Age (years) | n | 222 | 229 | 227 | 456 | 678 |
| | Mean ± SD | 21.1 ± 5.0 | 21.6 ± 6.5 | 21.9 ± 6.7 | 21.7 ± 6.6 | 21.5 ± 6.1 |
| | **p-value*** | | | **0.1277** | | |
| Sex | Female (n,%) | 148 (66.7) | 150 (65.5) | 139 (61.2) | 289 (63.4) | 437 (64.5) |
| | Male (n,%) | 74 (33.3) | 79 (34.5) | 88 (38.8) | 167 (36.6) | 241 (35.5) |
| | **p-value*** | | | **0.4010** | | |
| Ethnic origin | White/Caucasian (n,%) | 209 (94.1) | 220 (96.1) | 208 (91.6) | 428 (93.9) | 637 (94.0) |
| | Black (n,%) | 4 ( 1.8) | 1 ( 0.4) | 3 ( 1.3) | 4 ( 0.9) | 8 ( 1.2) |
| | Asian (n,%) | 9 ( 4.1) | 7 ( 3.1) | 13 ( 5.7) | 20 ( 4.4) | 29 ( 4.3) |
| | Other (n,%) | 0 ( 0.0) | 1 ( 0.4) | 3 ( 1.3) | 4 ( 0.9) | 4 ( 0.6) |
| | **p-value*** | | | **0.3811** | | |
| Height (cm) | n | 222 | 229 | 227 | 456 | 678 |
| | Mean ± SD | 168.9 ± 8.1 | 169.2 ± 8.6 | 170.4 ± 9.0 | 169.8 ± 8.8 | 169.5 ± 8.6 |
| | **p-value*** | | | **0.1978** | | |
| Weight (kg) | n | 222 | 229 | 227 | 456 | 678 |
| | Mean ± SD | 68.2 ± 10.9 | 67.7 ± 12.0 | 70.1 ± 13.4 | 68.9 ± 12.8 | 68.7 ± 12.2 |
| | **p-value*** | | | **0.4363** | | |
| BMI (kg/m²) | n | 222 | 229 | 227 | 456 | 678 |
| | Mean ± SD | 23.86 ± 3.33 | 23.58 ± 3.38 | 24.02 ± 3.58 | 23.80 ± 3.48 | 23.82 ± 3.43 |
| | **p-value*** | | | **0.8169** | | |

*Characteristics are compared between overall EPs® 7630 group and Placebo group using the t-test for quantitative variables and the chi-square test for qualitative variables.

**Results of the primary outcome criterion**

The occurrence of adverse drug reactions (ADRs) during the 4 months treatment, defined as the proportion of participants in each trial group with ADRs was the primary outcome criterion of this trial.

**Number of ADRs with onset during the active treatment phase (safety set)**

| | SAF | | | |
|---|---|---|---|---|
| | | EPs® 7630 | | |
| | Placebo (N=223) | 3x20 mg (N=230) | 3x20/40 mg (N=230) | Total (N=460) |
| **Subjects with ADRs** | [redacted] | [redacted] | [redacted] | [redacted] |
| **ADR(s)** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Percentage difference [%]** | | | | [redacted] |
| **Upper limit of one-sided 97.5% CI [%]** | | | | [redacted] |

The percentage difference was [redacted], with an upper limit of the one-sided 97.5% confidence interval of [redacted], which is XXXX than 10%. As a consequence, non-inferiority of the treatment with EPs® 7630 compared to placebo with respect to the ADR-rate could [redacted].

**Results of intake effect analysis**

The analysis of the intake effect was not the primary aim of this study. According to the results for the intake effects selected for this study following:

- Definition A defining common cold episodes according to Jawad et al. (Jawad et al. 2012) and
- Definition B defining a common cold episode as equivalent to the intake of the corresponding high dose (Box II) - 3 x 2 film-coated tablets

[redacted] between EPs® 7630 and placebo were observed under the setting of the present clinical trial.

**Results of safety analysis**

**Number and incidence of AEs and ADRs during active treatment, the post-treatment exposure phase and active treatment or post-treatment exposure phase (any causality, safety set)**

| | Placebo (N=223) | | | 3x20 mg (N=230) | | | EPs® 7630 3x20/40 mg (N=230) | | | Overall (N=460) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ae | exposition days | ir | ae | exposition days | ir | ae | exposition days | ir | ae | exposition days | ir |
| **Active treatment phase** | | | | | | | | | | | | |
| Any AEs | [redacted] | | | | | | | | | | | |
| Any ADRs | [redacted] | | | | | | | | | | | |
| **Post-treatment exposure phase** | | | | | | | | | | | | |
| Any AEs | [redacted] | | | | | | | | | | | |
| Any ADRs | [redacted] | | | | | | | | | | | |
| **Active treatment or post-treatment exposure phase** | | | | | | | | | | | | |
| Any AEs | [redacted] | | | | | | | | | | | |
| Any ADRs | [redacted] | | | | | | | | | | | |

ae: Number of AEs; ir: incidence rate calculated as follows: (number of events/number of exposition days)*100, ADR: adverse drug reaction
Suspected adverse event: causal relationship assessed as 'unlikely' [3], 'possible' [2] or 'probable' [1]
post-treatment exposure phase: within 7 days after last treatment with EPs® 7630

**Serious adverse events (safety set)**

[redacted] subjects, [redacted] male and X female subjects, receiving [redacted] had an SAE reported. All events were severe, too. [redacted] considered [redacted], and [redacted] relationship [redacted] considered [redacted].

**Other safety assessments**

No relevant changes could be detected in the assessment of laboratory parameters, vital signs, and physical examination between the beginning and the end of the treatment phase. Individually clinically relevant changes were reported as AEs.

**CONCLUSION**

This study was conducted as a prospective, monocentric, randomised, double-blind, placebo-controlled, phase III clinical trial. The main objective of the this clinical trial was to evaluate the safety of EPs® 7630 intake compared to placebo in adult subjects (≥ 18 years old) during a

long-term (4 months) treatment. Primary outcome criterion was therefore the occurrence of adverse drug reactions (ADRs), defined as the proportion of participants in each trial group with ADRs.

A total of 798 male and female subjects (≥ 18 years old) was screened for inclusion into this randomised monocentric safety study. A total of 720 subjects were randomised in a ratio of 2:1: 489 of them to receive EPs® 7630 and 239 to receive placebo for up to 4 months. All participants were healthy with no common cold symptoms at the time of randomisation.

During the active treatment phase, the proportion of participants who reported ADRs [redacted] in both the placebo ([redacted] ADRs in [redacted] ([redacted]) subjects) and the overall EPs® 7630 groups ([redacted] ADRs in [redacted] ([redacted]) subjects): The percentage difference was [redacted], with an upper limit of the one-sided 97.5% confidence interval of [redacted], which is [redacted] than the prespecified limit of 10%. As a consequence, [redacted] of the treatment with EPs® 7630 compared to placebo with respect to the ADR-rate was [redacted].

Overall, the number of subjects with AEs and SOCs/PTs most affected during the active treatment and during the post-treatment exposure phase was [redacted] in both treatment groups.

[redacted] in the [redacted] led to the withdrawal of the [redacted]. [redacted] treatment unrelated SAEs in [redacted] ([redacted]) were reported for the [redacted] during the active treatment phase; [redacted] led to the withdrawal of the subject.

During the additional post-treatment exposure phase, [redacted] with an intake of [redacted] reported an SAE ([redacted]), for which the causal relationship to the investigational medicinal product [redacted] assessed as '[redacted]'.

After the post-treatment exposure phase, [redacted] non-related AEs, [redacted], were reported.

Laboratory parameters and vital signs assessed after 4 months of treatment did not give raise to safety concerns with EPs® 7630.

Thus, the tolerability of treatment with EPs® 7630 was very good, which is in line with previous trials in adults with common cold (Lizogub et al., 2007; Keck et al., 2015).

Results for the intake effects selected for this trial as secondary outcome variables following:

- **Definition A** defining common cold episodes according to Jawad et al. (2012) and
- **Definition B** defining a common cold episode as equivalent to the intake of the corresponding high dose (Box II) - 3 x 2 film-coated tablets

[redacted] between EPs® 7630 and placebo intake under the present trial design. Due to the sparseness of empirical data in the population and this setting, no confirmatory hypotheses were formulated for these variables and the data were analysed descriptively.

In summary, these results show an excellent safety profile of a long-term treatment (4 months) which was the primary outcome variable. Therefore, EPs® 7630 is a well-tolerated medicinal product. The safety was [redacted] to that with the placebo with [redacted] in the intake effect between both treatments.

**References**

Jawad M, Schoop R, Suter A, Klein P, Eccles R. Safety and Efficacy Profile of Echinacea purpurea to Prevent Common Cold Episodes: A Randomized, Double-Blind, Placebo-Controlled Trial. Evidence-Based Complementary and Alternative Medicine 2012, vol. 2012, Article ID 841315, 7 pages. doi:10.1155/2012/841315.

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Lizogub VG, Riley DS, Heger M. Efficacy of a pelargonium sidoides preparation in patients with the common cold: a randomized, double blind, placebo-controlled clinical trial. Explore 2007; 3(6): 573-584.