Clinical trial results:
EPs® 7630 film-coated tablets in subjects (18 years old) suffering from common cold symptoms in a general practice setting.
A prospective, multi-center, single-arm, open-label, phase IV clinical post-marketing safety study

Summary

EudraCT number	2010-022441-21
Trial protocol	AT
Global end of trial date	22 August 2013

Results information

Result version number	v1 (current)
This version publication date	01 March 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	701004.01.012

Additional study identifiers

ISRCTN number	ISRCTN65790556
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Willmar Schwabe GmbH & Co. KG
Sponsor organisation address	Dr. Willmar Schwabe Str. 4, Karlsruhe, Germany, 76227
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Scientific contact	Clinical Research Department, Dr. Willmar Schwabe GmbH & Co. KG, +49 7214005573,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 August 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 August 2013
Global end of trial reached?	Yes
Global end of trial date	22 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the present post-marketing study is to gain further information about the safety and treatment outcome with EPs® 7630 film-coated tablets (Kaloba 20 mg Filmtabletten) in adult subjects (≥ 18 years old) suffering from common cold.

Protection of trial subjects:

Possibility to withdraw consent by patient. Monitoring of adverse events and laboratory parameters.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 January 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 120
Worldwide total number of subjects	120
EEA total number of subjects	120

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	120
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment
Recruitment details: -

Pre-assignment
Screening details: Subjects were recruited in eight investigational sites

Pre-assignment period milestones	
Number of subjects started	120
Number of subjects completed	120

Period 1	
Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	No
Arm title	Baseline

Arm description:

Baseline before starting EPs® 7630 treatment

Arm type	Baseline

No investigational medicinal product assigned in this arm

Arm title	EPs® 7630

Arm description:

Investigational medical product containing EPs® 7630, 20 mg per film-coated tablet (Kaloba 20 mg Filmtabletten)

Arm type	Experimental
Investigational medicinal product name	EPs® 7630
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 film-coated tablet 3 times a day for 10 consecutive days

Number of subjects in period 1	Baseline	EPs® 7630
Started	120	120
Completed	120	117
Not completed	0	3
Physician decision	-	1
Consent withdrawn by subject	-	1

Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period (overall period)
Reporting group description:	
Investigational medical product containing EPs® 7630, 20 mg per film-coated tablet (Kaloba 20 mg Filmtabletten)	

Reporting group values	Treatment period (overall period)	Total	
Number of subjects	120	120	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	120	120	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	38.9		
standard deviation	± 13.6	-	
Gender categorical			
Units: Subjects			
Female	84	84	
Male	36	36	

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full analysis set (FAS) consisted of all subjects having received study medication at least once and having at least one measurement of one of the efficiency parameters during the treatment period.	

Reporting group values	Full analysis set		
Number of subjects	120		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		

Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	120		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	38.9		
standard deviation	± 13.6		
Gender categorical			
Units: Subjects			
Female	84		
Male	36		

End points

End points reporting groups

Reporting group title	Baseline
Reporting group description:	
Baseline before starting EPs® 7630 treatment	
Reporting group title	EPs® 7630
Reporting group description:	
Investigational medical product containing EPs® 7630, 20 mg per film-coated tablet (Kaloba 20 mg Filmtabletten)	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full analysis set (FAS) consisted of all subjects having received study medication at least once and having at least one measurement of one of the efficiency parameters during the treatment period.	

Primary: Change in total score of common cold symptoms (CCS) between baseline and end of treatment as assessed by the investigator

End point title	Change in total score of common cold symptoms (CCS) between baseline and end of treatment as assessed by the investigator
End point description:	
Common cold symptoms: Nasal discharge, sore throat, nasal congestion, sneezing, scratchy throat, hoarseness, cough, headache, malaise, fever; each symptom assessed according to a 4-point verbal rating scale from "0 = not present" to "3 = severe". Note: There were no primary end points defined for analysis. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.	
End point type	Primary
End point timeframe:	
Baseline and end of Treatment (10-day Treatment period)	

End point values	Baseline	EPs® 7630		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	117		
Units: points				
arithmetic mean (standard deviation)	10.8 (± 3.6)	2.2 (± 2.5)		

Statistical analyses

Statistical analysis title	Non-parametric analysis
Statistical analysis description:	
Baseline and end of treatment values available for 117 subjects with arithmetic mean (standard deviation) of change between baseline and end of treatment: -8.6 (±4.0) points; LOCF, two-sided . The number of subjects included in analysis was summarized to 237 (Baseline 120, End of treatment 117) because of requirements of the Eudra-CT data base.	
Comparison groups	Baseline v EPs® 7630

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001
Method	Wilcoxon signed-rank test

Notes:

[1] - Within-subject change between baseline and end of treatment

Primary: Change in further common cold relevant complaints between baseline and end of treatment as assessed by the investigator

End point title	Change in further common cold relevant complaints between baseline and end of treatment as assessed by the investigator

End point description:

Further common cold relevant complaints: Pulmonary rates at auscultation, sputum production, chest pain during coughing, chilliness, exhaustion, loss of appetite, diarrhea, muscle aches;
each symptom assessed according to a 4-point verbal rating scale from "0 = not present" to "3 = severe"
Note: There were no primary end points defined for analysis. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.

End point type	Primary

End point timeframe:

Baseline and end of Treatment (10-day Treatment period)

End point values	Baseline	EPs® 7630		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	117		
Units: points				
arithmetic mean (standard deviation)	3.4 (± 2.7)	0.5 (± 1.3)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects with arithmetic mean (standard deviation) of change between baseline and end of treatment: -2.8 (±2.6) points; LOCF, two-sided. The number of subjects included in analysis was summarized to 237 (Baseline 120, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v EPs® 7630
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.0001
Method	Wilcoxon signed-rank test

Notes:

[2] - Within-subject change between baseline and end of treatment

Primary: Change in total score of common cold symptoms and further common cold

relevant complaints between baseline and end of treatment as assessed by the investigator

End point title	Change in total score of common cold symptoms and further common cold relevant complaints between baseline and end of treatment as assessed by the investigator

End point description:

Common cold symptoms: Nasal discharge, sore throat, nasal congestion, sneezing, scratchy throat, hoarseness, cough, headache, malaise, fever;
Further common cold relevant complaints: Pulmonary rates at auscultation, sputum production, chest pain during coughing, chilliness, exhaustion, loss of appetite, diarrhea, muscle aches;
each symptom assessed according to a 4-point verbal rating scale from "0 = not present" to "3 = severe"
Note: There were no primary end points defined for analysis. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.

End point type	Primary

End point timeframe:

Baseline and end of Treatment (10-day Treatment period)

End point values	Baseline	EPs® 7630		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	117		
Units: points				
arithmetic mean (standard deviation)	14.2 (± 5.4)	2.8 (± 3.4)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects with arithmetic mean (standard deviation) of change between baseline and end of treatment: -11.4 (±5.6) points; LOCF, two-sided. The number of subjects included in analysis was summarized to 237 (Baseline 120, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v EPs® 7630
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.0001
Method	Wilcoxon signed-rank test

Notes:

[3] - Within-subject change between baseline and end of treatment

Primary: Change in common cold symptoms (CCS) as rated by the subject in the subject's diary

End point title	Change in common cold symptoms (CCS) as rated by the subject in the subject's diary

End point description:

15 common cold symptoms (not comparable with the common cold symptoms assessed by the investigator): Runny nose, sore throat, congested nose, sneezing, scratchy throat, hoarseness, cough, headache, malaise, chilliness, chest pain during coughing, lost of appetite, restless sleep, limited usual

daily activity, muscle aches;
each symptom rated by the subject according to a 5-point rating scale from "0 = not present" to "4 = severe".
Note: There were no primary end points defined for analysis. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.

End point type	Primary

End point timeframe:

Baseline and Day 10 (10-day Treatment period)

End point values	Baseline	EPs® 7630		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111[4]	92[5]		
Units: points				
arithmetic mean (standard deviation)	22.1 (± 9.6)	3.8 (± 4.2)		

Notes:

[4] - 111 subjects assessed CCS at Day 1 (baseline)

[5] - 92 subjects assessed CCS at Day 10

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Day 1 and Day 10 values available for 84 subjects with arithmetic mean (standard deviation) of change between Day 1 and Day 10: -18.2 (±9.7) points; two-sided. The number of subjects included in analysis was summarized to 203 (Baseline 111, End of treatment 92) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v EPs® 7630
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.0001
Method	Wilcoxon signed-rank test

Notes:

[6] - Within-subject change between Day 1 (baseline) and Day 10

Primary: Need for subject’s treatment with antibiotics according to the medical decision of the investigator

End point title	Need for subject’s treatment with antibiotics according to the medical decision of the investigator

End point description:

Subjects needed to be treated with antibiotics during the study are identified based on concomitant medication documentation.
Note: There were no primary end points defined for analysis. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.

End point type	Primary

End point timeframe:

Baseline and end of Treatment (10-day Treatment period)

End point values	Baseline	EPs® 7630		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120[7]	120		
Units: Subjects	0	2		

Notes:

[7] - Need for subject's treatment with antibiotics not evaluated at baseline

Statistical analyses

Statistical analysis title	Proportion of subjects

Statistical analysis description:

The proportion of subjects with need for treatment with antibiotics was identified with respect to the total study period and was based on all 120 subjects with EPs® 7630 Treatment. The number of subjects included in analysis was summarized to 240 (Baseline 120, End of treatment 120) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v EPs® 7630
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	percentage
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	5.9

Notes:

[8] - Proportion of subjects and exact 95% confidence interval for the proportion

Primary: Number of subjects who are 'not sick' or 'very mildly sick' as rated by the subject in the subject's diary

End point title	Number of subjects who are 'not sick' or 'very mildly sick' as rated by the subject in the subject's diary

End point description:

Possible answer to the question "How sick do you feel today?" in the subject's diary: 'not present', 'very mild', 'mild', 'moderate', 'severe'.
Note: There were no primary end points defined for analysis. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.

End point type	Primary

End point timeframe:

Day 1 (Baseline) and Day 10 (10-day treatment period)

End point values	Baseline	EPs® 7630		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	92		
Units: Subjects	17	87		

Statistical analyses

Statistical analysis title	Proportion of subjects

Statistical analysis description:

The proportion of subjects who are not sick or very mildly sick was calculated for the number of subjects with answer to the question "How sick do you feel today?" at Day 10 (in total, 92 subjects). The number of subjects included in analysis was summarized to 203 (Baseline 111, End of treatment 92) because of requirements of the Eudra-CT data base.

Comparison groups	EPs® 7630 v Baseline
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	percentage
Point estimate	94.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	87.8
upper limit	98.2

Notes:

[9] - Proportion of subjects and exact 95% confidence interval for the proportion

Primary: Treatment outcome according to the Integrative Medicine Outcome Scale (IMOS) as assessed by the investigator

End point title	Treatment outcome according to the Integrative Medicine Outcome Scale (IMOS) as assessed by the investigator

End point description:

The IMOS describes the general health status of the subject.
Note: There were no primary end points defined for analysis. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.

End point type	Primary

End point timeframe:

Assessment at end of Treatment (10-day Treatment period)

End point values	Baseline	EPs® 7630		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120[10]	117		
Units: Subjects				
Complete recovery	0	49		
Major improvement	0	49		
Slight to moderate improvement	0	16		

No change	0	3		
Deterioration	0	0		

Notes:

[10] - Assessment of treatment outcome not applicable at baseline

Statistical analyses

Statistical analysis title	Proportion of subjects with complete recovery

Statistical analysis description:

Treatment outcome according to IMOS as assessed by the investigator available for 117 subjects at the end of the treatment period; LOCF. The number of subjects included in analysis was summarized to 237 (Baseline 120, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v EPs® 7630
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	Percentage
Point estimate	41.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	32.8
upper limit	51.4

Notes:

[11] - Proportion of subjects and exact 95% confidence interval for proportion

Primary: Treatment outcome according to the Integrative Medicine Outcome Scale (IMOS) as assessed by the subject

End point title	Treatment outcome according to the Integrative Medicine Outcome Scale (IMOS) as assessed by the subject

End point description:

The IMOS describes the general health status of the subject.
Note: There were no primary end points defined for analysis. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.

End point type	Primary

End point timeframe:

Assessment at Day 10 (10-day Treatment period)

End point values	Baseline	EPs® 7630		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120[12]	90[13]		
Units: Subjects				
Complete recovery	0	39		
Major improvement	0	36		
Slight to moderate improvement	0	10		
No change	0	5		
Deterioration	0	0		

Notes:

[12] - Assessment of treatment outcome not applicable at baseline

[13] - Data available for 90 subjects at Day 10

Statistical analyses

Statistical analysis title	Proportion of subjects with complete recovery

Statistical analysis description:

Treatment outcome according to IMOS as assessed by the subject available for 90 subjects at the end of the treatment period (Day 10). The number of subjects included in analysis was summarized to 210 (Baseline 120, End of treatment 90) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v EPs® 7630
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other[14]
Parameter estimate	Percentage
Point estimate	43.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	32.9
upper limit	54.2

Notes:

[14] - Proportion of subjects with complete recovery and exact 95% confidence interval for the proportion

Primary: Satisfaction of the subject with the treatment according to the Integrative Medicine Patient Satisfaction Scale (IMPSS) as assessed by the subject in the subject's diary

End point title	Satisfaction of the subject with the treatment according to the Integrative Medicine Patient Satisfaction Scale (IMPSS) as assessed by the subject in the subject's diary

End point description:

The IMPSS uses a 5 point scale ranging from ‘very satisfied’ to ‘not satisfied at all’.
Note: There were no primary end points defined for analysis. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.

End point type	Primary

End point timeframe:

Assessment at Day 10 (10-day Treatment period)

End point values	Baseline	EPs® 7630		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120[15]	120		
Units: Subjects				
Very satisfied	0	38		
Satisfied	0	37		
Neutral	0	24		
Dissatisfied	0	1		

Very dissatisfied	0	1		
Not documented/ missing	0	19		

Notes:

[15] - Rating of satisfaction with treatment not applicable at baseline

Statistical analyses

Statistical analysis title	Proportion of subjects 'very satisfied'

Statistical analysis description:

Satisfaction with treatment according to IMPSS as assessed by the subject at Day 10 of the 10-day treatment period available for 120 subjects. The number of subjects included in analysis was summarized to 240 (Baseline 120, End of treatment 120) because of requirements of the Eudra-CT data base.

Comparison groups	EPs® 7630 v Baseline
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	other[16]
Parameter estimate	Percentage
Point estimate	31.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.5
upper limit	40.8

Notes:

[16] - Proportion of subjects 'very satisfied' with treatment and exact 95% confidence interval for the proportion

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 10.5 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups	
Reporting group title	No active treatment
Reporting group description: No active treatment	
Reporting group title	EPs 7630
Reporting group description: Verum treatment	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Overall, 15 subjects experienced non-serious adverse events. This number could not be entered into the database, because each adverse event occurred with a frequency which did not exceed the frequency threshold of 5% for reporting non-serious adverse events. Therefore, the number of subjects with non-serious adverse events resulted in 0 when considering the 5% frequency threshold.

Serious adverse events	No active treatment	EPs 7630	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 120 (0.83%)	0 / 120 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Thyroidectomy			
subjects affected / exposed	1 / 120 (0.83%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	No active treatment	EPs 7630	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 120 (0.00%)	0 / 120 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2010	Amendment No. 1: Study Protocol: modification of the study title; Informed consent and Patient information: elimination of footnote 1: modification of point 3 and point 6; CRF: modification of the study title; nasal examination severe (right and left) is an exclusion; pharyngeal swab was changed in nasal brushing; modification of assessment of integrative medicine outcome scale (IMOS); Patient Diaries: were expanded by muscle pain on page 5, 6, 7, 9, 10, 12, 13 (diary1) and page 5, 7, 8, 9, 10, 11, 13 (diary 2).
28 September 2011	Amendment No. 2: Study protocol: extension of study Duration to 23 months; modification of trial schedule (Visit 1 and Visit 3); Further specification of the "AE" Definition and Duration of treatment.
20 December 2012	Amendment No. 3: Study protocol: extension of study Duration to 35 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported