Clinical trial results:
A Phase 4, Randomised, Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate Efficacy of Isoprinosine® in Comparison With Placebo in Subjects With Confirmed Acute Respiratory Viral Infections due to Influenza A or B Virus, Respiratory Syncytial Virus, Adenovirus, or Parainfluenza Virus 1 or 3.

Summary

EudraCT number	2014-001863-11
Trial protocol	CZ SK
Global end of trial date	03 June 2015

Results information

Result version number	v1 (current)
This version publication date	02 June 2016
First version publication date	02 June 2016
Summary attachment (see zip file)	Justification to ERROR - Subject analysis set: Safety Analasys Set/EudrraCT_Letterhead.pdf (Letterhead_signed.pdf)

Trial information

Trial identification

Sponsor protocol code	EWO-ISO-2014/1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ewopharma AG
Sponsor organisation address	Vordergasse 43, Schaffhausen, Switzerland, CH-8200
Public contact	Medical Director, Ewopharma International, s.r.o., +421 2594 298 25, e.salpova@ewopharma.com
Scientific contact	Medical Director, Ewopharma International, s.r.o., +421 2594 298 25, e.salpova@ewopharma.com

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	01 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2015
Global end of trial reached?	Yes
Global end of trial date	03 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical efficacy of Isoprinosine compared with placebo in subjects with laboratory confirmed acute respiratory viral infections due to influenza A or B virus, respiratory syncytial virus (RSV), adenovirus, or parainfluenza virus 1 or 3.

Protection of trial subjects:

The tablets could be crushed and dissolved in a small amount of flavoured liquid at the time of administration as a meassure to make ingestion easier.
Study site staff also worked with the subject to determine acceptable times for dosing so that doses were taken approximately 8 hours apart and were consistent with the subject's lifestyle; scheduling of dosing did not disturb the subject's usual sleep patterns.

Background therapy:

Subjects were allowed to take symptomatic antipyretics and analgesics as required.

Evidence for comparator:

Randomisation and blinding were used to minimise bias in assessing subjective symptoms of influenza-like illness. The use of placebo in this study was justified because influenza-like illness is largely mild and self-limiting with no other treatments approved for acute respiratory viral infections other than influenza. Also, the use of influenza-specific antivirals (neuraminidase inhibitors or amantadine) is not a part of routine medical management of influenza-like illness in the countries in which the study was conducted.

Actual start date of recruitment	08 December 2014
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	Czech Republic: 159
Country: Number of subjects enrolled	Slovakia: 304
Worldwide total number of subjects	463
EEA total number of subjects	463

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)	438
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 25 study sites both in Czech Republic (14 sites) and Slovakia (11 sites). Due to the delay in enrolling first subject as a result of late flu alert (not before December 2014) it was decided to continue enrolling more subjects until 30 April 2015 so as to have maximum number of completed subjects.

Pre-assignment

Screening details:

Laboratory confirmed acute respiratory viral infections due to influenza A or B virus, respiratory syncytial virus, adenovirus, or parainfluenza virus 1 or 3. Had an influenza-like illness according predefined measures and had onset of influenza-like illness no more than 36 hours prior to screening. Did not meet any of exclusion criteria.

Pre-assignment period milestones

Number of subjects started	480[1]
Number of subjects completed	463

Pre-assignment subject non-completion reasons

Reason: Number of subjects	screenfailure: 15
Reason: Number of subjects	non-randomized: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subject who have started the pre-assignment period is bigger due that more patients had been screened before being randomized

Period 1

Period 1 title	Randomisation visit, EOT, overall period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Placebo tablets were identical in appearance to Isoprinosine tablets. Isoprinosine tablets and matching placebo tablets were provided in the identical cartons identified by a kit number such that all study site staff and subjects remained blinded throughout the study. Only personnel in IWRS and clinical supplies were unblinded. Each subject was assigned a randomisation number that was separate from the subject identification number.

Arms

Are arms mutually exclusive?	Yes
Arm title	Isoprinosine tablets 500-mg tablets

Arm description:

Subjects self-administered two tablets of Isoprinosine (500 mg) orally three times daily

Arm type	Experimental
Investigational medicinal product name	Isoprinosine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two tablets of Isoprinosine (500 mg) orally three times daily, seven-day dosing duration period (Day 1 to Day 7)

Arm title	Placebo

Arm description:

Subjects self-administered two tablets of placebo orally three times daily

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

placebo two tablets orally three times daily, seven day administration period

Number of subjects in period 1	Isoprinosine tablets 500-mg tablets	Placebo
Started	231	232
Completed	226	230
Not completed	5	2
Consent withdrawn by subject	2	1
Adverse event, non-fatal	1	1
non-compliance with the protocol	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Isoprinosine tablets 500-mg tablets
Reporting group description:	
Subjects self-administered two tablets of Isoprinosine (500 mg) orally three times daily	
Reporting group title	Placebo
Reporting group description:	
Subjects self-administered two tablets of placebo orally three times daily	

Reporting group values	Isoprinosine tablets 500-mg tablets	Placebo	Total
Number of subjects	231	232	463
Age categorical			
Study population: male or nonpregnant female subject aged 18 to 75 years			
Units: Subjects			
Adults (18-64 years)	219	219	438
From 65-84 years	12	13	25
Age continuous			
A summary of demographics and baseline information were presented by treatment group and overall. The demographic characteristics consisted of age (years), sex, fertility status (female only), baseline weight, baseline height, and baseline body mass index (BMI).			
Units: years			
median	40	40	
standard deviation	± 12.86	± 13.45	-
Gender categorical			
Male or nonpregnant female subject aged 18 to 75 years;			
Units: Subjects			
Female	111	107	218
Male	120	125	245
Subject group by age and BMI			
Non-obese/obese subjects of less or more than 50 years of age (≥ <50)			
Units: Subjects			
obese (BMI ≥30 kg/m2) subjects of less than 50 y	29	25	54
Non-obese (BMI <30 kg/m2) subjects of less than 50y	136	142	278
non-obese (BMI <30 kg/m2) subjects ≥50 y	45	44	89
obese (BMI ≥30 kg/m2) subjects ≥50 y	21	21	42

Subject analysis sets	
Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
mITT analysis set consists of all subjects randomly assigned to study drug who had a positive laboratory confirmation of acute respiratory viral infection due to influenza A or B virus, respiratory syncytial virus, adenovirus, or parainfluenza virus 1 or 3. This is the analysis set used for evaluating the primary efficacy objective. 137 subjects were included in the mITT analysis set. The mITT analysis set is used as the primary efficacy analysis set.	

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol analysis set consists of subjects in the mITT analysis set with an EOT assessment that received the randomised study drug, took at least 80% of the prescribed doses of study drug, and did not have any major protocol deviations.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT analysis set consists of all subjects who were randomly assigned to receive double-blinded study drug. All analyses using the ITT set groups subjects according to randomised treatment.

Reporting group values	mITT	PP	ITT
Number of subjects	137	116	463
Age categorical			
Study population: male or nonpregnant female subject aged 18 to 75 years			
Units: Subjects			
Adults (18-64 years)			438
From 65-84 years			25
Age continuous			
A summary of demographics and baseline information were presented by treatment group and overall. The demographic characteristics consisted of age (years), sex, fertility status (female only), baseline weight, baseline height, and baseline body mass index (BMI).			
Units: years			
median			40
standard deviation	±	±	± 13.15
Gender categorical			
Male or nonpregnant female subject aged 18 to 75 years;			
Units: Subjects			
Female			218
Male			245
Subject group by age and BMI			
Non-obese/obese subjects of less or more than 50 years of age (≥ <50)			
Units: Subjects			
obese (BMI ≥30 kg/m2) subjects of less than 50 y			54
Non-obese (BMI <30 kg/m2) subjects of less than 50y			278
non-obese (BMI <30 kg/m2) subjects ≥50 y			89
obese (BMI ≥30 kg/m2) subjects ≥50 y			42

End points

End points reporting groups

Reporting group title	Isoprinosine tablets 500-mg tablets
Reporting group description:	
Subjects self-administered two tablets of Isoprinosine (500 mg) orally three times daily	
Reporting group title	Placebo
Reporting group description:	
Subjects self-administered two tablets of placebo orally three times daily	
Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
mITT analysis set consists of all subjects randomly assigned to study drug who had a positive laboratory confirmation of acute respiratory viral infection due to influenza A or B virus, respiratory syncytial virus, adenovirus, or parainfluenza virus 1 or 3. This is the analysis set used for evaluating the primary efficacy objective. 137 subjects were included in the mITT analysis set. The mITT analysis set is used as the primary efficacy analysis set.	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-protocol analysis set consists of subjects in the mITT analysis set with an EOT assessment that received the randomised study drug, took at least 80% of the prescribed doses of study drug, and did not have any major protocol deviations.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT analysis set consists of all subjects who were randomly assigned to receive double-blinded study drug. All analyses using the ITT set groups subjects according to randomised treatment.	

Primary: the time to resolution of all influenza-like symptoms presented at baseline to none

End point title	the time to resolution of all influenza-like symptoms presented at baseline to none
End point description:	
The time to resolution was calculated as the total number of days from randomisation to first instance where all influenza-like symptoms had a score of 0 (date of resolution of all influenza like symptoms minus date of randomisation + 1). The subject used the daily diary card to document the symptoms on each day and continued beyond the EOT visit up to and including the follow-up visit on Day 21. The first day where it was observed that all symptoms had a score of 0 was flagged for analysis.	
End point type	Primary
End point timeframe:	
Subjects will record the presence of influenza like illness respiratory and constitutional symptoms once daily in the evening using the 4 point scale on subject diary cards total number of days from randomisation up to and including the follow up.	

End point values	Isoprinosine tablets 500-mg tablets	Placebo	mITT	ITT
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	71	66	116	463
Units: days				
Time to Resolution of all Influenza-like Symptoms	8	8	8	8

Statistical analyses

Statistical analysis title	SAP Version 1.0

Statistical analysis description:

Summary information on the number of subjects with resolution of symptoms, the number of censored subjects, median and quartile survival time and the corresponding value for the log rank test were presented. Treatment effect was estimated by calculating the hazard ratio (HR) and its 95% CI from an unstratified proportional hazards model. The assumption of proportional hazards underlying the log-rank test was investigated.

Comparison groups	Isoprinosine tablets 500-mg tablets v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.324 [2]
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	1.175
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.806
upper limit	1.714
Variability estimate	Standard deviation

Notes:

[1] - Continuous data were described using descriptive statistics (i.e. n, mean, standard deviation [SD], median, minimum, and maximum). Categorical data were described using the subject count and percentage in each category. All statistical tests were 2-sided hypothesis tests performed using a 5% level of significance, leading to 95% (2-sided) confidence intervals (CIs).

[2] - If a P value was less than 0.001, it was reported as '<0.001'. If a value was greater than 0.999, it was reported as '>0.999'.

Primary: the time to resolution of all influenza-like symptoms

End point title	the time to resolution of all influenza-like symptoms

End point description:

Primary endpoint was analysed for the ITT analysis set for the subgroups based on BMI (BMI <30 kg/m2, BMI ≥30 kg/m2).
Primary endpoint was displayed by the combination of subgroup of interest and age group, where age group was <50 years and ≥ 50 years.

End point type	Primary

End point timeframe:

Subjects will record the presence of influenza like illness respiratory and constitutional symptoms once daily in the evening using the 4 point scale on subject diary cards total number of days from randomisation up to and including the follow up.

End point values	Isoprinosine tablets 500-mg tablets	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	136	142	278	
Units: days				
median (confidence interval 95%)				
Age Group: <50 BMI <30	8 (7 to 10)	8 (7 to 12)	8 (7 to 12)	

Statistical analyses

Statistical analysis title	SAP Version 1.0

Statistical analysis description:

The analysis was conducted on the ITT analysis set and consisted of an unstratified log-rank test to compare the time to resolution of all influenza-like symptoms presented at baseline to none between Isoprinosine and placebo. Any ties in the data were handled by the discrete method.

Comparison groups	Isoprinosine tablets 500-mg tablets v Placebo
Number of subjects included in analysis	278
Analysis specification	Post-hoc
Analysis type	superiority[3]
P-value	= 0.018
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	1.307
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.691
Variability estimate	Standard deviation

Notes:

[3] - Treatment effect was estimated by calculating the hazard ratio (HR) and its 95% CI from an unstratified proportional hazards model.

Primary: the time to resolution of all influenza-like symptoms

End point title	the time to resolution of all influenza-like symptoms

End point description:

Primary endpoint was analysed for the ITT analysis set for the subgroups based on BMI (BMI <30 kg/m2, BMI ≥30 kg/m2).
Primary endpoint was displayed by the combination of subgroup of interest and age group, where age group was <50 years and ≥ 50 years.

End point type	Primary

End point timeframe:

Subjects will record the presence of influenza like illness respiratory and constitutional symptoms once daily in the evening using the 4 point scale on subject diary cards total number of days from randomisation up to and including the follow up.

End point values	Isoprinosine tablets 500-mg tablets	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	29	25	54	
Units: days				
median (confidence interval 95%)				
Age Group: <50 BMI ≥30	8 (7 to 16)	7 (7 to 9)	7.5 (7 to 16)	

Statistical analyses

Statistical analysis title	SAP Version 1.0

Statistical analysis description:

The analysis was conducted on the ITT analysis set and consisted of an unstratified log-rank test to compare the time to resolution of all influenza-like symptoms presented at baseline to none between Isoprinosine and placebo. Any ties in the data were handled by the discrete method.

Comparison groups	Isoprinosine tablets 500-mg tablets v Placebo
Number of subjects included in analysis	54
Analysis specification	Post-hoc
Analysis type	superiority[4]
P-value	= 0.37
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.782
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.429
upper limit	1.426
Variability estimate	Standard deviation

Notes:

[4] - Treatment effect was estimated by calculating the hazard ratio (HR) and its 95% CI from an unstratified proportional hazards model.

Primary: the time to resolution of all influenza-like symptoms

End point title	the time to resolution of all influenza-like symptoms

End point description:

Primary endpoint was analysed for the ITT analysis set for the subgroups based on BMI (BMI <30 kg/m2, BMI ≥30 kg/m2).
Primary endpoint was displayed by the combination of subgroup of interest and age group, where age group was <50 years and ≥ 50 years.

End point type	Primary

End point timeframe:

Subjects will record the presence of influenza like illness respiratory and constitutional symptoms once daily in the evening using the 4 point scale on subject diary cards total number of days from randomisation up to and including the follow up.

End point values	Isoprinosine tablets 500-mg tablets	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	45	44	89	
Units: days				
median (confidence interval 95%)				
Age Group: ≥50 BMI <30	8 (8 to 11)	8 (7 to 10)	8 (8 to 11)	

Statistical analyses

Statistical analysis title	SAP Version 1.0

Statistical analysis description:

The analysis was conducted on the ITT analysis set and consisted of an unstratified log-rank test to compare the time to resolution of all influenza-like symptoms presented at baseline to none between Isoprinosine and placebo. Any ties in the data were handled by the discrete method.

Comparison groups	Placebo v Isoprinosine tablets 500-mg tablets
Number of subjects included in analysis	89
Analysis specification	Post-hoc
Analysis type	superiority[5]
P-value	= 0.383
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.838
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.534
upper limit	1.316
Variability estimate	Standard deviation

Notes:

[5] - Treatment effect was estimated by calculating the hazard ratio (HR) and its 95% CI from an unstratified proportional hazards model.

Primary: the time to resolution of all influenza-like symptoms

End point title	the time to resolution of all influenza-like symptoms

End point description:

Primary endpoint was analysed for the ITT analysis set for the subgroups based on BMI (BMI <30 kg/m2, BMI ≥30 kg/m2).
Primary endpoint was displayed by the combination of subgroup of interest and age group, where age group was <50 years and ≥ 50 years.

End point type	Primary

End point timeframe:

Subjects will record the presence of influenza like illness respiratory and constitutional symptoms once daily in the evening using the 4 point scale on subject diary cards total number of days from randomisation up to and including the follow up.

End point values	Isoprinosine tablets 500-mg tablets	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	21	21	42	
Units: days				
median (confidence interval 95%)				
Age Group: ≥50 BMI ≥30	10 (8 to 12)	8 (8 to 11)	9 (8 to 16)	

Statistical analyses

Statistical analysis title	SAP Version 1.0

Statistical analysis description:

The analysis was conducted on the ITT analysis set and consisted of an unstratified log-rank test to compare the time to resolution of all influenza-like symptoms presented at baseline to none between Isoprinosine and placebo. Any ties in the data were handled by the discrete method.

Comparison groups	Placebo v Isoprinosine tablets 500-mg tablets
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority[6]
P-value	= 0.37
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.782
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.429
upper limit	1.426
Variability estimate	Standard deviation

Notes:

[6] - Treatment effect was estimated by calculating the hazard ratio (HR) and its 95% CI from an unstratified proportional hazards model.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed from the time the subject signs the informed consent until exit from the study (day 21 +/- 3 days)

Adverse event reporting additional description:

Safety assessments included monitoring AEs, serious AEs (SAEs), and AEs leading to treatment interruption or discontinuation. The number of subjects included in Safety Analysis Set is corresponding with the number of subjects who were given at least one dose of study treatment – 464 subjects.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Isoprinosine treatment group

Reporting group description:

All percentages were based on the number of subjects on the actual treatment in the ITT analysis set for isoprinosine treatment group.

Reporting group title	Placebo treatment group

Reporting group description:

All percentages were based on the number of subjects on the actual treatment in the ITT analysis set for placebo treatment group.

Serious adverse events	Isoprinosine treatment group	Placebo treatment group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 229 (0.44%)	1 / 235 (0.43%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Pleuropneumonia	Additional description: Study Day 5, the subject experienced a severe serious adverse event of pleuropneumonia. Study drug permanently discontinued.The investigator assessed the serious adverse event of pleuropneumonia to be unrelated to study drug.		
subjects affected / exposed	1 / 229 (0.44%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 39	0 / 48	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
vertebrogenic pain syndrome	Additional description: Subject in the Isoprinosine treatment group experienced severe treatment-emergent SAEs of rhinopharyngitis and vertebrogenic pain syndrome that led to the permanent discontinuation of study drug, and the subject discontinued from the study.		

subjects affected / exposed	1 / 229 (0.44%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 39	0 / 48	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Isoprinosine treatment group	Placebo treatment group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 229 (17.03%)	48 / 235 (20.43%)	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Hypotension			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 229 (0.87%)	3 / 235 (1.28%)	
occurrences (all)	39	48	
Influenza-like symptoms			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Mucous discharge			
subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Pain menstrual			
subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Premenstrual pain			

subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Respiratory, thoracic and mediastinal disorders			
Bronchoconstriction			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Cough			
subjects affected / exposed	0 / 229 (0.00%)	2 / 235 (0.85%)	
occurrences (all)	39	48	
Hemoptysis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Irritative cough			
subjects affected / exposed	1 / 229 (0.44%)	3 / 235 (1.28%)	
occurrences (all)	39	48	
Nasal mucosal swelling			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Nasal obstruction			
subjects affected / exposed	3 / 229 (1.31%)	2 / 235 (0.85%)	
occurrences (all)	39	48	
Shortness of breath			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Nervous system disorders			
Cervicobrachial syndrome			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Headache			
subjects affected / exposed	2 / 229 (0.87%)	2 / 235 (0.85%)	
occurrences (all)	39	48	
Ear and labyrinth disorders			

Earache			
subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Motion sickness			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Sensation of pressure in ear			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Tinnitus			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Vertigo			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Eye disorders			
Eyelid rash			
subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	1 / 229 (0.44%)	5 / 235 (2.13%)	
occurrences (all)	39	48	
Diarrhoea			
subjects affected / exposed	1 / 229 (0.44%)	2 / 235 (0.85%)	
occurrences (all)	39	48	
Dyspepsia			
subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Nausea			
subjects affected / exposed	1 / 229 (0.44%)	2 / 235 (0.85%)	
occurrences (all)	39	48	
Pyrosis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Rectal bleeding			

subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Stomatitis aphthous			
subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Vomiting			
subjects affected / exposed	1 / 229 (0.44%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Skin and subcutaneous tissue disorders			
Efflorescence			
subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Rash			
subjects affected / exposed	1 / 229 (0.44%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Skin rash			
subjects affected / exposed	0 / 229 (0.00%)	2 / 235 (0.85%)	
occurrences (all)	39	48	
Musculoskeletal and connective tissue disorders			
Cervicocranial syndrome			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Joint pain			
subjects affected / exposed	1 / 229 (0.44%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Muscle cramps			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Muscle pain			
subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Vertebrogenic pain syndrome			
subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Infections and infestations			

Paronychia			
subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Pharyngitis			
subjects affected / exposed	1 / 229 (0.44%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Pharyngotonsillitis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Pneumonia			
subjects affected / exposed	1 / 229 (0.44%)	2 / 235 (0.85%)	
occurrences (all)	39	48	
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 229 (0.00%)	2 / 235 (0.85%)	
occurrences (all)	39	48	
Rhinitis			
subjects affected / exposed	1 / 229 (0.44%)	2 / 235 (0.85%)	
occurrences (all)	39	48	
Rhinopharyngitis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Rhinosinusitis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 235 (0.43%)	
occurrences (all)	39	48	
Sinusitis			
subjects affected / exposed	0 / 229 (0.00%)	3 / 235 (1.28%)	
occurrences (all)	39	48	
Superinfection bacterial			
subjects affected / exposed	0 / 229 (0.00%)	3 / 235 (1.28%)	
occurrences (all)	39	48	
Tonsillitis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 235 (0.00%)	
occurrences (all)	39	48	
Tracheitis			
subjects affected / exposed	1 / 229 (0.44%)	1 / 235 (0.43%)	
occurrences (all)	39	48	

Metabolism and nutrition disorders Iron deficiency subjects affected / exposed occurrences (all)	 1 / 229 (0.44%) 39	 0 / 235 (0.00%) 48	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2014	Protocol amendment Version 1 dated 29 May 2014.: Inclusion criterion 1: Upper age limit was changed from 55 years to 75 years.; Inclusion criterion 2: Influenza-like illness definition was expanded to include self-measured axillary temperature of ≥37.5°C; Recording of daily activities assessment on additional diary cards after the EOT visit was included in case of subjects issued with additional diary cards at the EOT visit; Clarification was added for recording oral temperature, influenza-like symptoms, and ability to perform activities of daily living after the EOT visit on additional diary cards in case of subjects presenting with fever, a score of 1 or more on influenza-like symptoms assessment scale, or a score of 1 or more on daily activities assessment scale at the EOT visit. Clarification was also added regarding the resolution criteria for these 3 parameters after the EOT visit.; Body weight and height were moved from 'demographics and other baseline characteristics' section to 'Vital sign measurements' section for consistency with the schedule of events.; A section for influenza-like symptoms assessment on Day 1 prior to randomisation was added for clarity.; The section for 'review of concomitant medications' was updated to include prior medications as well.; Adverse event assessment was changed to only to be assessed from the time the subject signs the informed consent form (ICF) until exit from the study.; Serious adverse event assessment was amended such that those that occurred after the subject exited the study need not be reported.; Serious adverse event reporting text was amended to include electronic data capture (EDC) system and fax line number was corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The impact of the lack of significant influenza outbreak adversely affected the statistical power and reduced the power of the study and the results of the study were impacted by epidemiologic considerations.

Notes: