



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 measure 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/m ²) subjects of less than 50 y | 29 | 25 | 54 |
| Non-obese (BMI <30 kg/m ²) subjects of less than 50y | 136 | 142 | 278 |
| non-obese (BMI <30 kg/m ²) subjects ≥50 y | 45 | 44 | 89 |
| obese (BMI ≥30 kg/m ²) 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 | | | 40 |
| median | | | |
| 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 (\geq <50) | | | |
| Units: Subjects | | | |
| obese (BMI \geq 30 kg/m ²) subjects of less than 50 y | | | 54 |
| Non-obese (BMI <30 kg/m ²) subjects of less than 50y | | | 278 |
| non-obese (BMI <30 kg/m ²) subjects \geq 50 y | | | 89 |
| obese (BMI \geq 30 kg/m ²) subjects \geq 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/m ² , BMI ≥30 kg/m ²). | |
| 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/m ² , BMI ≥30 kg/m ²). | |
| 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/m ² , BMI ≥30 kg/m ²). | |
| 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/m ² , BMI ≥ 30 kg/m ²). | |
| 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 occurrences (all) | 1 / 229 (0.44%) 39 | 0 / 235 (0.00%) 48 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchoconstriction subjects affected / exposed occurrences (all) | 0 / 229 (0.00%) 39 | 1 / 235 (0.43%) 48 | |
| Cough subjects affected / exposed occurrences (all) | 0 / 229 (0.00%) 39 | 2 / 235 (0.85%) 48 | |
| Hemoptysis subjects affected / exposed occurrences (all) | 0 / 229 (0.00%) 39 | 1 / 235 (0.43%) 48 | |
| Irritative cough subjects affected / exposed occurrences (all) | 1 / 229 (0.44%) 39 | 3 / 235 (1.28%) 48 | |
| Nasal mucosal swelling subjects affected / exposed occurrences (all) | 0 / 229 (0.00%) 39 | 1 / 235 (0.43%) 48 | |
| Nasal obstruction subjects affected / exposed occurrences (all) | 3 / 229 (1.31%) 39 | 2 / 235 (0.85%) 48 | |
| Shortness of breath subjects affected / exposed occurrences (all) | 0 / 229 (0.00%) 39 | 1 / 235 (0.43%) 48 | |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 1 / 229 (0.44%) 39 | 0 / 235 (0.00%) 48 | |
| Nervous system disorders | | | |
| Cervicobrachial syndrome subjects affected / exposed occurrences (all) | 0 / 229 (0.00%) 39 | 1 / 235 (0.43%) 48 | |
| Headache subjects affected / exposed occurrences (all) | 2 / 229 (0.87%) 39 | 2 / 235 (0.85%) 48 | |
| Ear and labyrinth disorders | | | |

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|---|
| 29 May 2014 | <p>Protocol amendment Version 1 dated 29 May 2014.: Inclusion criterion 1: Upper age limit was changed from 55 years to 75 years.;</p> <p>Inclusion criterion 2: Influenza-like illness definition was expanded to include self-measured axillary temperature of $\geq 37.5^{\circ}\text{C}$;</p> <p>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;</p> <p>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.;</p> <p>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.;</p> <p>A section for influenza-like symptoms assessment on Day 1 prior to randomisation was added for clarity.;</p> <p>The section for 'review of concomitant medications' was updated to include prior medications as well.;</p> <p>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.;</p> <p>Serious adverse event assessment was amended such that those that occurred after the subject exited the study need not be reported.;</p> <p>Serious adverse event reporting text was amended to include electronic data capture (EDC) system and fax line number was corrected.</p> |

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: