



Clinical trial results:

A randomized, double-blind, parallel group, placebo controlled Phase II study to evaluate the safety and efficacy of inhaled LASAG and Placebo, applied three times daily in adult hospitalized patients with acute serious influenza

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2012-004072-19 |
| Trial protocol | DE CZ HU SK ES LV LT BG |
| Global end of trial date | 15 May 2015 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 31 March 2021 |
| First version publication date | 18 May 2016 |
| Version creation reason | <ul style="list-style-type: none">Changes to summary attachments New version of PDF without the scanned signatures. Done for security purposes so that no scanned signature are available in public domain. |
| Summary attachment (see zip file) | CSR Summary (059a_Acti-INSP-001_Clinical Study Report_(Summary)_V01_20160411_no_signature_page_.pdf) |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | Acti-INSP-001 |
|-----------------------|---------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Vectura GmbH |
| Sponsor organisation address | Robert-Koch-Allee 29, Gauting, Germany, 82131 |
| Public contact | Project Manager Clinical Studies, Ventaleon GmbH Wohraer Str. 37 35285 Gemünden/Wohra, 0049 64535853043, karlheinz.nocker@ventaleon.com |
| Scientific contact | Chief Medical Officer Dr. Sebastian Canisius, Ventaleon GmbH Wohraer Str. 37 35285 Gemünden/Wohra, 0049 64535853048, sebastian.canisius@ventaleon.com |

Notes:

Paediatric regulatory details

| | |
|---------------------------------------|----|
| Is trial part of an agreed paediatric | No |
|---------------------------------------|----|

| | |
|--|----|
| investigation plan (PIP) | |
| 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 | 17 February 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 May 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 May 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy and safety of inhaled D,L-lysine acetylsalicylate glycine (LASAG) plus standard of care compared to placebo plus standard of care in patients hospitalized due to acute serious influenza OR an influenza caused worsening of a primary medical condition measured by time to alleviation of influenza symptoms.

Influenza symptoms are defined as:

- nasal congestion
- sore throat
- cough
- aches/myalgia
- fatigue
- headaches
- feverishness/chills/sweats

Time to alleviation is defined as the time in hours from first inhalation of LASAG until at least 5 of 7 clinical influenza symptoms are rated with 0 (not present, i.e. like before the influenza) or 1 (mild) on the influenza symptom questionnaire without any use of symptom relief medication (i.e. acetaminophen) and remained so for at least 24±2 hours.

Protection of trial subjects:

Based on the data from preclinical and clinical testing as well as information from the routine clinical use of Acetyl-Salicylic Acid (ASA) it is highly probable that patients suffering from acute serious influenza could benefit from intake of the study medication. Potential risk of lacking efficacy is minimized by allowed usage of standard care, for all patients, according to routine practice of each participating site. All adverse events, including those previously observed during the initial clinical exposure, will be carefully monitored three times daily during the whole treatment period and daily until follow-up visit 3. Additionally, vital signs, physical examinations, O2 saturation and laboratory parameters will be recorded to maximize patient's safety.

Indicated, permitted antiviral treatment must have been started prior to first LASAG inhalation (and will then be continued). Initiation of antiviral treatment or any change in its dosing during the treatment period will lead to withdrawal of the patient.

As usage of NSAIDs is not allowed, only acetaminophen must be used as influenza symptom relief medication during study treatment. Patients treated with a daily dose of ≤ 100mg Aspirin for Coronary Artery Disease (CAD) prevention may be included, but the Aspirin dose must remain unchanged during the course of the study.

Background therapy:

Antiviral medications:

Indicated, permitted antiviral treatment must have been started prior to first LASAG inhalation (and will then be continued). Initiation of antiviral treatment or any change in its dosing during the treatment period will lead to withdrawal of the patient.

o Antiviral therapy with adamantane derivatives is allowed. However, antiviral therapy with adamantane derivatives is usually not effective because of widespread resistance of influenza viruses

against these agents.

o Antiviral therapy with neuraminidase blocking agents: If antiviral therapy is indicated to the investigator's opinion the following neuraminidase blocking agents is allowed: Oseltamivir

o Zanamivir is prohibited as it is administered via inhalation and interactions with the study drug LASAG cannot be excluded.

If patients receive Oseltamivir as standard of care at the respective study site, this treatment should be continued during hospital stay according to Oseltamivir's label for a minimum of 5 days. If standard of care at the respective site does not include Oseltamivir treatment, only symptomatic treatment may be initiated (i.e. acetaminophen) at investigators' discretion.

Antibiotic Treatment

Antibiotic Treatment is not prohibited but, as usual, there must be a clear indication for its use. A prophylactic administration to avoid bacterial infection and / or pneumonia is not considered as such a clear indication and should therefore be avoided. Any antibiotic treatment needs to be documented in the patient's records and in the eCRF.

Evidence for comparator:

N/A as comparator is placebo.

| | |
|---|-----------------|
| Actual start date of recruitment | 26 January 2013 |
| 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 | Slovakia: 1 |
| Country: Number of subjects enrolled | Spain: 10 |
| Country: Number of subjects enrolled | Czech Republic: 9 |
| Country: Number of subjects enrolled | Germany: 2 |
| Country: Number of subjects enrolled | Latvia: 1 |
| Country: Number of subjects enrolled | Lithuania: 3 |
| Country: Number of subjects enrolled | Romania: 89 |
| Worldwide total number of subjects | 115 |
| EEA total number of subjects | 115 |

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) | 97 |
| From 65 to 84 years | 18 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment started in the norther hemisphere in Germany (Europe), and the southern hemisphere was subsequently added.

Pre-assignment

Screening details:

During periods of documented influenza in the community, subjects with influenza-like illness meeting all inclusion and none of the exclusion criteria were enrolled and randomized prior to laboratory confirmation of influenza. Subjects outside of periods of documented community influenza had to have RT-PCR or RAT confirmation prior to randomization

Pre-assignment period milestones

| | |
|------------------------------|--------------------|
| Number of subjects started | 171 ^[1] |
| Number of subjects completed | 115 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|------------------|
| Reason: Number of subjects | Not eligible: 56 |
|----------------------------|------------------|

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: We reported also the number of patients screened (171) but a certain amount was not eligible and therefore was never recruited really.

Period 1

| | |
|------------------------------|---------------------------|
| Period 1 title | Baseline (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|-------------|
| Arm title | LASAG group |
|------------------|-------------|

Arm description:

800 mg LASAG/4mL fill dose is equivalent to 400 mg ASA/4 mL fill dose. 400mg ASA/4mL fill dose results in an alveolar dose of 45mg ASA.

| | |
|--|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | LASAG |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Subjects will receive 15 doses of study medication by AKITA JET nebulizer on 5 to 6 consecutive days. Usually, three doses per day will be applied, depending on the start time of the first inhalation.

Start of Treatment can then consist of either:

- o 3 inhalations starting with morning inhalation between 7:00 – 9:00
- o 2 inhalations starting with mid-day inhalation between 12:00 – 14:00
- o 1 inhalation starting with evening inhalation between 17:00 – 19:00

This is depending on the time the patient can be randomized.

| | |
|------------------|---------------|
| Arm title | Placebo Group |
|------------------|---------------|

Arm description:

4 mL saline solution (0.9% Sodium chloride (NaCl)).

| | |
|--|---------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Isotonic Saline |
| Investigational medicinal product code | |
| Other name | Placebo |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Subjects will receive 15 doses of study medication by AKITA JET nebulizer on 5 to 6 consecutive days.

Start of Treatment can then consist of either:

- o 3 inhalations starting with morning inhalation between 7:00 – 9:00
- o 2 inhalations starting with mid-day inhalation between 12:00 – 14:00
- o 1 inhalation starting with evening inhalation between 17:00 – 19:00

This is depending on the time the patient can be randomized.

| | |
|------------------|----------------|
| Arm title | LASAG low dose |
|------------------|----------------|

Arm description:

400 mg LASAG/4mL fill dose is equivalent to 200 mg/4mL ASA fill dose. 200 mg/4mL ASA fill dose results in an alveolar dose of 27mg ASA.

| | |
|--|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | LASAG low dose |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Subjects will receive 15 doses of study medication by AKITA JET nebulizer on 5 to 6 consecutive days.

Usually, three doses per day will be applied, depending on the start time of the first inhalation.

Start of Treatment can then consist of either:

- o 3 inhalations starting with morning inhalation between 7:00 – 9:00
- o 2 inhalations starting with mid-day inhalation between 12:00 – 14:00
- o 1 inhalation starting with evening inhalation between 17:00 – 19:00

This is depending on the time the patient can be randomized.

| Number of subjects in period 1 | LASAG group | Placebo Group | LASAG low dose |
|---------------------------------------|-------------|---------------|----------------|
| Started | 57 | 52 | 6 |
| Completed | 37 | 31 | 4 |
| Not completed | 20 | 21 | 2 |
| No inhalation of study drug | 1 | 1 | - |
| No Influenza Infection confirmed | 11 | 15 | 2 |
| Protocol deviation | 8 | 5 | - |

Baseline characteristics

Reporting groups

| | |
|---|----------------|
| Reporting group title | LASAG group |
| Reporting group description: 800 mg LASAG/4mL fill dose is equivalent to 400 mg ASA/4 mL fill dose. 400mg ASA/4mL fill dose results in an alveolar dose of 45mg ASA. | |
| Reporting group title | Placebo Group |
| Reporting group description: 4 mL saline solution (0.9% Sodium chloride (NaCl)). | |
| Reporting group title | LASAG low dose |
| Reporting group description: 400 mg LASAG/4mL fill dose is equivalent to 200 mg/4mL ASA fill dose. 200 mg/4mL ASA fill dose results in an alveolar dose of 27mg ASA. | |

| Reporting group values | LASAG group | Placebo Group | LASAG low dose |
|---|-------------|---------------|----------------|
| Number of subjects | 57 | 52 | 6 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 42.84 | 45.85 | 53.33 |
| standard deviation | ± 13.31 | ± 16.87 | ± 11.24 |
| Gender categorical Units: Subjects | | | |
| Female | 30 | 29 | 2 |
| Male | 27 | 23 | 4 |
| Not recorded | 0 | 0 | 0 |
| Influenza positive (RT-PCR) | | | |
| An RT-PCR was performed to determine whether a subject enrolled really had an Influenza infection. The MITT was defined as the subjects having Influenza infection. | | | |
| Units: Subjects | | | |
| Influenza positive | 46 | 38 | 5 |
| Influenza negative | 11 | 14 | 1 |
| Reporting group values | Total | | |
| Number of subjects | 115 | | |

| | | | |
|---|----|--|--|
| 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) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 61 | | |
| Male | 54 | | |
| Not recorded | 0 | | |
| Influenza positive (RT-PCR) | | | |
| An RT-PCR was performed to determine whether a subject enrolled really had an Influenza infection. The MITT was defined as the subjects having Influenza infection. | | | |
| Units: Subjects | | | |
| Influenza positive | 89 | | |
| Influenza negative | 26 | | |

Subject analysis sets

| | |
|--|-----------------------------|
| Subject analysis set title | Safety Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| The safety analysis set (SA) includes all subjects randomized in the trial who received at least one inhalation. Treatment groups for the SA will be defined by real treatments of patients. | |
| Subject analysis set title | MITT Set |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: | |
| Modified intent-to-treat (MITT) population consisted of all subjects who received at least one dose of study drug (or an inhalation of placebo) and who had influenza infection confirmed by RT-PCR. | |
| Subject analysis set title | PP Set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| The per protocol (PP) analysis set included all subjects from the MITT population who had at least 13 inhalations of LASAG or placebo and had no major protocol deviations (identified prior to database lock and unblinding). | |

| Reporting group values | Safety Set | MITT Set | PP Set |
|------------------------------------|------------|----------|--------|
| Number of subjects | 113 | 81 | 68 |
| Age categorical Units: Subjects | | | |
| In utero | | | |

| | | | |
|--|------------------|------------------|------------------|
| Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years arithmetic mean standard deviation | 44.55 ± 15.85 | 44.94 ± 15.46 | 44.04 ± 14.51 |
| Gender categorical Units: Subjects | | | |
| Female | 59 | 46 | 38 |
| Male | 54 | 35 | 30 |
| Not recorded | 0 | 0 | 0 |
| Influenza positive (RT-PCR) | | | |
| An RT-PCR was performed to determine whether a subject enrolled really had an Influenza infection. The MITT was defined as the subjects having Influenza infection. | | | |
| Units: Subjects | | | |
| Influenza positive | 85 | 81 | 68 |
| Influenza negative | 28 | 0 | 0 |

End points

End points reporting groups

| | |
|---|-----------------------------|
| Reporting group title | LASAG group |
| Reporting group description: 800 mg LASAG/4mL fill dose is equivalent to 400 mg ASA/4 mL fill dose. 400mg ASA/4mL fill dose results in an alveolar dose of 45mg ASA. | |
| Reporting group title | Placebo Group |
| Reporting group description: 4 mL saline solution (0.9% Sodium chloride (NaCl)). | |
| Reporting group title | LASAG low dose |
| Reporting group description: 400 mg LASAG/4mL fill dose is equivalent to 200 mg/4mL ASA fill dose. 200 mg/4mL ASA fill dose results in an alveolar dose of 27mg ASA. | |
| Subject analysis set title | Safety Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The safety analysis set (SA) includes all subjects randomized in the trial who received at least one inhalation. Treatment groups for the SA will be defined by real treatments of patients. | |
| Subject analysis set title | MITT Set |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: Modified intent-to-treat (MITT) population consisted of all subjects who received at least one dose of study drug (or an inhalation of placebo) and who had influenza infection confirmed by RT-PCR. | |
| Subject analysis set title | PP Set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The per protocol (PP) analysis set included all subjects from the MITT population who had at least 13 inhalations of LASAG or placebo and had no major protocol deviations (identified prior to database lock and unblinding). | |

Primary: Time to alleviation of clinical influenza symptoms

| | |
|---|---|
| End point title | Time to alleviation of clinical influenza symptoms ^[1] |
| End point description: The primary variable was the time to alleviation of clinical influenza symptoms which was defined as the time in hours from first inhalation of LASAG until at least 5 of 7 clinical influenza symptoms were rated with 0 (not present, i.e. like before the influenza) or 1 (mild) on the influenza symptom questionnaire without any use of symptom relief medication (i.e. acetaminophen) and remained so for at least 24±2 hours. | |
| End point type | Primary |
| End point timeframe: From first inhalation of study drug until first occurrence of alleviation of symptoms defined as at least 5 of 7 clinical influenza symptoms rated with 0 or 1 without any symptom relief medication and remained so for at least 24±2 hrs. | |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The arm "low dose" was discontinued prematurely. Therefore results for this arm for the endpoints are not reported.

| End point values | LASAG group | Placebo Group | MITT Set | PP Set |
|--------------------------------------|---------------------|---------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 39 | 34 | 73 | 67 |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 43.03 (\pm 26.6) | 42.2 (\pm 28.63) | 42.64 (\pm 27.37) | 43.28 (\pm 25.87) |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Kaplan-Meier estimation of time to alleviation [h]/Kaplan-Meier |
|-----------------------------------|---|

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Primary analysis |
| Statistical analysis description: The difference between treatment groups calculated by means of a t-Test (two-sided). | |
| Comparison groups | LASAG group v Placebo Group |
| Number of subjects included in analysis | 73 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | = 0.65 ^[3] |
| Method | Logrank |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.0653 |
| upper limit | 13.7213 |
| Variability estimate | Standard deviation |
| Dispersion value | 27.5589 |

Notes:

[2] - This is the primary analysis of time to alleviation between LASAG Group and Placebo Group in the MITT analysis set.

[3] - one-sided p-value

Secondary: Time to alleviation of clinical influenza signs

| | |
|---|--|
| End point title | Time to alleviation of clinical influenza signs ^[4] |
| End point description: | |
| End point type | Secondary |
| End point timeframe: First inhalation until end of treatment | |

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The arm "low dose" was discontinued prematurely. Therefore results for this arm for the endpoints are not reported.

| End point values | LASAG group | Placebo Group | MITT Set | |
|--------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 39 | 31 | 70 | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 26.58 (\pm 20.65) | 33.58 (\pm 24.56) | 29.68 (\pm 22.57) | |

Statistical analyses

| Statistical analysis title | Comparison between LASAG and Placebo |
|---|--------------------------------------|
| Statistical analysis description: Two Sided T-Test | |
| Comparison groups | LASAG group v Placebo Group |
| Number of subjects included in analysis | 70 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2 |
| Method | t-test, 1-sided |
| Parameter estimate | Mean difference (final values) |

Secondary: Change in routine daily activity score

| End point title | Change in routine daily activity score ^[5] |
|---|---|
| End point description: The efficacy of LASAG and placebo was investigated in addition by routine daily activity score on a functional visual analogue scale ranging from 0 (unable to perform one's routine daily activities at all) to 10 (fully able to perform one's routine daily activities). This score was integrated in the influenza symptom questionnaire. Scores had to be measured by a regular ruler starting from 0 to the nearest 0.1 cm and be documented together with date and time. The baseline corrected area under these daily activity score curve (AUC) was calculated for each patient and standardized by division through the time interval of the underlying measurements. Missing values were imputed by LOCF (last observation carried forward). | |
| End point type | Secondary |

End point timeframe:

Activity scores were filled out prior to each inhalation (i.e. mostly on a 3-times per day) during the treatment phase, once daily during each follow-up visit and three times daily during the daily visit after termination of treatment.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The arm "low dose" was discontinued prematurely. Therefore results for this arm for the endpoints are not reported.

| End point values | LASAG group | Placebo Group | | |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 36 | | |
| Units: points | | | | |
| arithmetic mean (standard deviation) | 3.2 (\pm 1.64) | 2.69 (\pm 1.46) | | |

Statistical analyses

| | |
|--|--------------------------------------|
| Statistical analysis title | Comparison between LASAG and Placebo |
| Statistical analysis description: The improvement of the daily activity scores was analyzed by the Mann-Whitney U-test. | |
| Comparison groups | LASAG group v Placebo Group |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[6] |
| P-value | = 0.25 |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[6] - The improvement of the daily activity scores was more pronounced in the LASAG group (mean and median of 3.2) compared with the placebo group (mean and median of 2.7). The difference between both treatment groups was small however (mean difference 0.51) and the Mann-Whitney U-test yielded a non significant $p=0.25$.

Secondary: Anti-viral efficacy

| | |
|-----------------|------------------------------------|
| End point title | Anti-viral efficacy ^[7] |
|-----------------|------------------------------------|

End point description:

Since no quantitative values for viral load were available, a qualitative analysis of viral load prior to 8th inhalation was performed. The RT-PCR prior to 8th inhalation determined the influenza status of the patients (negative/positive). The test was performed for 76 patients of the MITT set, excluding patients #0701-001 (LASAG group, stopped after inhalation 2), #1002-005 (LASAG group, stopped after inhalation 4) and #1006-010 (LASAG group, stopped after inhalation 5). Additionally, patient #0306-001 (LASAG group) and patient #0901-001 (placebo group) were excluded because no RT-PCR data were obtained.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Number of patients with positive influenza RT-PCR test prior to inhalation 8

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The arm "low dose" was discontinued prematurely. Therefore results for this arm for the endpoints are not reported.

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | LASAG group | Placebo Group | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 41 | 35 | | |
| Units: number of pts. | 15 | 15 | | |

Statistical analyses

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | Comparison between LASAG and Placebo |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Comparison of percentage of patients who still have positive Influenza RT-PCR test prior to inhalation 8

(MITT). Per definition, all patients in MITT had a positive Influenza RT-PCR test at baseline.

| | |
|---|-----------------------------|
| Comparison groups | LASAG group v Placebo Group |
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[8] |
| P-value | = 0.58 ^[9] |
| Method | Chi-squared |

Notes:

[8] - The number of patients with negative RT-PCR at inhalation 8 was slightly larger in the LASAG group (63% LASAG vs. 57% placebo).

[9] - The chi-squared test performed showed no statistically significant difference between LASAG and placebo group (two sided Chi-squared test: p-value=0.58).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After signing ICF until 30 days after the end of Follow-Up Visit 3, serious adverse events will be collected by Investigator and reported to Sponsor. Adverse Events will be collected until the end of Follow-Up Visit 3.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 18.0 |

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | LASAG group |
|-----------------------|-------------|

Reporting group description:

800 mg LASAG/4mL fill dose is equivalent to 400 mg ASA/4 mL fill dose. 400mg ASA/4mL fill dose results in an alveolar dose of 45mg ASA.

| | |
|-----------------------|---------------|
| Reporting group title | Placebo Group |
|-----------------------|---------------|

Reporting group description:

4 mL saline solution (0.9% Sodium chloride (NaCl)).

| | |
|-----------------------|----------------|
| Reporting group title | LASAG low dose |
|-----------------------|----------------|

Reporting group description:

400 mg LASAG/4mL fill dose is equivalent to 200 mg/4mL ASA fill dose. 200 mg/4mL ASA fill dose results in an alveolar dose of 27mg ASA.

| Serious adverse events | LASAG group | Placebo Group | LASAG low dose |
|---|--|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 51 (1.96%) | 0 / 6 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Infections and infestations | | | |
| Respiratory tract infection nosokomial | Additional description: Event was a respiratory nosocomial infection. It was considered as SAE due to a prolongation of hospitalization. This event occurred in the placebo group. | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 51 (1.96%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | LASAG group | Placebo Group | LASAG low dose |
|---|------------------|------------------|----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 23 / 56 (41.07%) | 21 / 51 (41.18%) | 5 / 6 (83.33%) |

| | | | |
|---|------------------------|----------------------|---------------------|
| Vascular disorders Hypotension/Hypertension subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 2 | 4 / 51 (7.84%) 4 | 0 / 6 (0.00%) 0 |
| General disorders and administration site conditions Influenza Symptoms subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 3 / 51 (5.88%) 3 | 0 / 6 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Dyspnea/Epistaxis/Pneumonia subjects affected / exposed occurrences (all) | 10 / 56 (17.86%) 10 | 4 / 51 (7.84%) 4 | 2 / 6 (33.33%) 2 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 1 / 51 (1.96%) 1 | 1 / 6 (16.67%) 1 |
| Investigations Different Investigations subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 2 | 0 / 51 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Cardiac disorders Bradycardia subjects affected / exposed occurrences (all) | 1 / 56 (1.79%) 1 | 0 / 51 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 3 | 4 / 51 (7.84%) 4 | 2 / 6 (33.33%) 2 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 56 (1.79%) 1 | 0 / 51 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Gastrointestinal disorders Diarrhoea/Nausea/Gastritis subjects affected / exposed occurrences (all) | 10 / 56 (17.86%) 14 | 8 / 51 (15.69%) 9 | 1 / 6 (16.67%) 1 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|----------------------|------------------------|---------------------|
| Exanthema subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 2 / 51 (3.92%) 2 | 0 / 6 (0.00%) 0 |
| Renal and urinary disorders Renal insufficiency subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 1 / 51 (1.96%) 1 | 0 / 6 (0.00%) 0 |
| Infections and infestations Respiratory Tract Infections subjects affected / exposed occurrences (all) | 7 / 56 (12.50%) 7 | 12 / 51 (23.53%) 12 | 1 / 6 (16.67%) 1 |
| Metabolism and nutrition disorders Abnormal Lab Values subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 2 / 51 (3.92%) 2 | 0 / 6 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 29 September 2014 | <p>The protocol has been amended due to an administrative change. The sponsor Activaero GmbH with its principal place of business at Wohraer Strasse 37, 35285 Gemuenden/Wohra, Germany, has been acquired by the company Vectura Group plc (UK). As a result of this acquisition Activaero GmbH has been re-named to Vectura GmbH. The protocol is amended to discontinue the investigation of the LASAG low dose arm (i.e. 400mg LASAG /4 mL, three times daily). An additional amendment to the protocol is performed with regard to a change in the inclusion criterion 9 (see below). However, due to the fact that LASAG's antiviral effect is affecting the host cell and not the virus cell itself, the effectiveness with regard to virus reduction can still be assumed even after 72 hours (=3 days) of symptom onset. This hypothesis was supported in preclinical efficacy models which demonstrated that LASAG was efficacious in animal models with established infection (Activaero GmbH, IB 2012). For this reason the inclusion criterion 9 is changed so that a patient reported onset of illness less than 120 hours (=5 days) before first study drug application is eligible.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported