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	v1
This version publication date	18 May 2016
First version publication date	18 May 2016
Summary attachment (see zip file)	Acti-INSP-001 Clinical Study Report Summary V01 (059a_Acti-INSP-001_Clinical Study Report _(Summary)_V01_20160411_F_signed.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 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	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 derivates is allowed. However, antiviral therapy with adamantane derivates 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: The number 171 is the number of screened subjects. Our understanding of the number of patients in the pre-assignment period is to mention here the total number of screened subjects. These subjects were not enrolled in the study, but screened for eligibility (i.e. influenza symptoms as indicated by inclusion/exclusion criteria). Only subjects in the pre-assignment period (115) were really enrolled.

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	44.55	44.94	44.04
standard deviation	± 15.85	± 15.46	± 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 third arm, low dose LASAG, has been terminated as per substantial amendment to the protocol on 29 Sept 2014. In that amendment it was decided that the endpoint analysis will only be done for the comparison of LASAG (formerly LASAG High Dose) vs. Placebo. Therefore, not results for the comparison with low dose LASAG are reported here. Additional data can be found in full CSR.

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 (± 26.6)	42.2 (± 28.63)	42.64 (± 27.37)	43.28 (± 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 third arm, low dose LASAG, has been terminated as per substantial amendment to the protocol on 29 Sept 2014. In that amendment it was decided that the endpoint analysis will only be done for the comparison of LASAG (formerly LASAG High Dose) vs. Placebo. Therefore, not results for the comparison with low dose LASAG are reported here. Additional data can be found in full CSR.

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 (± 20.65)	33.58 (± 24.56)	29.68 (± 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 third arm, low dose LASAG, has been terminated as per substantial amendment to the protocol on 29 Sept 2014. In that amendment it was decided that the endpoint analysis will only be done for the comparison of LASAG (formerly LASAG High Dose) vs. Placebo. Therefore, not results for the comparison with low dose LASAG are reported here. Additional data can be found in full CSR.

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 (± 1.64)	2.69 (± 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 inflzenza 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 third arm, low dose LASAG, has been terminated as per substantial amendment to the protocol on 29 Sept 2014. In that amendment it was decided that the endpoint analysis will only be done for the comparison of LASAG (formerly LASAG High Dose) vs. Placebo. Therefore, not results for the comparison with low dose LASAG are reported here. Additional data can be found in full CSR.

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2014	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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported