Clinical Study Report
Final

Clinical Trial:

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

Acronym: Acti-INSP-001

EudraCT-Number: 2012-004072-19

Phase II Study – Proof of Concept Dose Finding

Study Sponsor:

Vectura GmbH

Robert-Koch-Allee 29

82131 Gauting, Germany

Tel.: 0049-89-897969-0

Legal Owner of study data:

Ventaleon GmbH

Wohraer Strasse 37

Gemuenden/Wohra, Germany

Tel.: 0049-6453-58530-40

1 TITLE PAGE

Study title:
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

Name of test drug/ investigational product:
LASAG for inhalation

Indication studied:
Influenza

Design of the study.
Placebo controlled randomized double blind multicenter comparison

Name of the sponsor:
Vectura GmbH, Robert-Koch-Allee 29, 82131 Gauting, Germany

Name of legal owner of study data:
Ventaleon GmbH, Wohraer Str. 37, 35285 Gemünden/Wohra, Germany

Protocol identification (code or number):
Acti-INSP-001 - EudraCT-Number: 2012-004072-19

Development phase of study:
Phase II Study – Proof of Concept Dose Finding

Study initiation date, first patient enrolled:
January 26th, 2013

Date of early study termination:
May 06th, 2015 (early termination by sponsor decision due to slow enrolment)

Study completion date (last patient completed):
May 15th, 2015

Name and affiliation of sponsor's responsible medical officer
Sebastian Canisius, MD, PhD, EU-QPPV
Telephone: 0049-6453-58530-48 Fax: 0049-6453-58530-50
E-mail: Sebastian.Canisius@ventaleon.com

Name of legal owner signatory:
Gerhard Scheuch, PhD
Telephone: 0049-6453-58530-40 - E-mail: gerhard.scheuch@bio-inhalation.com

Name of Sponsor signatory:
Jeremy Matson
Telephone: 0044-1249-667719 – E-Mail: Jeremy.matson@vectura.com

General statement:
The study was performed in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP) and the applicable law. This includes the archiving of essential documents.

Date of the report:
April 11th, 2016

1.1 Signatures

Study title: 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

This clinical study report has been produced in concordance with the principles of good clinical practice with special respect to guidelines ICH E3, E6 and E9.

By signing this report we certify that it provides a true and accurate record of the conduct of this study and its results.

Sebastian Canisius*, MD, PhD, EU-QPPV
Ventaleon GmbH, Wohraer Strasse 37, 35285 Gemuenden/Wohra, Germany

14 APR 16 _____
Date Dr. Sebastian Canisius

Gerhard Scheuch*, PhD,

14. Apr. 16 _____
Date Dr. Gerhard Scheuch

Karlheinz Nocker*, PhD
Ventaleon GmbH, Wohraer Strasse 37, 35285 Gemuenden/Wohra, Germany

14. Apr. 16 _____
Date Dr. Karlheinz Nocker

Jeremy Matson

Vectura Ltd., One Prospect West, Chippenham, Wiltshire, SN14 6FH, United Kingdom

14 APR 16 _____
Date Jeremy Matson

* Employed by Vectura at the time the study was carried out, now employed by Ventaleon GmbH, the legal owner of the study results.

2 SYNOPSIS

This Report was dedicated to the main analysis, i.e. the evaluation of the LASAG group (800 mg LASAG/4mL fill dose equivalent to 400 mg ASA/4 mL fill dose) compared to placebo applied to patients with positive influenza test according to clinical study protocol V2.3 (29 Sep 14 incl. amendment 1).

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Title of study**:**

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

Investigators and Study Centers:

Site No. 0101 Hospital San Roque Infectious Diseases Service Bajada Pucará 1900 5000 Cordoba ARGENTINA	Site No. 0102 Sanatorio Mayo Privado S.A Infectious Diseases Committee Humberto Primo 520 X5000FAL Cordoba ARGENTINA
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Site No. 0108 Hospital Británico de Buenos Aires Pulmonary department Perdriel 74 1280 Buenos Aires ARGENTINA	Site No. 0109 Sanatorio Güemes Pulmonary department F. A. de Figueroa 1240 C1180AAX Buenos Aires ARGENTINA
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Bajada Pucara 2025 5000 Cordoba ARGENTINA	Av. Belgrano 1746 C1093AAS C.A.B.A. ARGENTINA
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Site No. 0115 Clinica de Especialidades Villa Maria Corrientes 733, Villa Maria Cordoba ARGENTINA	Site No. 0116 Clinica Modelo Moron Rep. Oriental del Uruguay 224 - Moron B1708JFF Moron ARGENTINA
Site No. 0201 Hospital San Martin Concepción # 1050 Quillota - Chile 2260494 Quillota CHILE	Site No. 0203 Hospital Regional de Talca Uno Norte # 1990 Talca - Chile 3460001 Talca CHILE
Site No. 0205 Hospital Base de Curico Chacabuco # 121 Curico CHILE	
Site No. 0301 Krajská zdravotní, a.s. - Masarykova nemocnice Ústí nad Labem Department of infectious diseases Socialni pece 3316/12A 401 13 Usti nad Labem CZECH REPUBLIC	Site No. 0302 Nemocnice Mělník Department of infectious diseases Pražská 528 27601 Mělník CZECH REPUBLIC
Site No. 0304 Nemocnice Tábor, a.s. Department of pulmonary Kpt. Jaroše 2000 39002 Tábor CZECH REPUBLIC	Site No. 0305 Nemocnice Nové Město na Moravě, příspěvková organizace department of Internal Medicine Žďárská 610 592 31 Nove Město na Morave CZECH REPUBLIC
Site No. 0306	Site No. 0307

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Nemocnice Blansko Pulmonary department Sadová 33 67831 Blansko CZECH REPUBLIC	Krajská zdravotní, a.s. - Nemocnice Teplice, o.z department of Internal Medicine Duchcovská 53 415 29 Teplice CZECH REPUBLIC
Site No. 0308 Nemocnice Na Bulovce Department of infectious diseases Budínova 2 18000 Prague CZECH REPUBLIC	
Site No. 0401 Medizinische Hochschule Hannover Klinik für Pneumologie Carl-Neuberg-Straße 1 30625 Hannover GERMANY	Site No. 0403 Universitätsmedizin Rostock, Forschung und Lehre Klinik und Poliklinik für Innere Medizin, Abteilung für Tropenmedizin und Infektionskrankheiten Ernst-Heydemann-Str. 6 18057 Rostock GERMANY
Site No. 0404 Klinik für Pneumologie, Thoraxonkologie und Beatmungsmedizin Mathias Spital Frankenburgstr. 31 48431 Rheine GERMANY	Site No. 0405 Klinikum Ibbenbüren GmbH Klinik für Pneumologie, Thoraxonkologie und Beatmungsmedizin Schulstr. 11 49477 Ibbenbüren GERMANY
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Site No. 0503 University of Pecs 1st Department of Internal medicine Ifjusag Str. 13 7624 Pecs HUNGARY	Site No. 0504 Hetenyi Geza Hospital Infectology department Toszegi ut 21 H-S004 Szolnok HUNGARY

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Site No. 0601 Voivodeship Infectious Diseases Hospital Third Department Wolska 37 01-201 Warszawa POLAND	Site No. 0602 Medical University of Łódź Pulmonological and Allergological Clinical Ward Kopcińskiego 22 90-153 Łódź POLAND
Site No. 0603 SP ZOZ Specialist Hospital in Puławy Observational and Infectious Diseases Ward for adults ul. Bema 1 24-100 Puławy POLAND	Site No. 0604 Voivodeship Specialist Hospital in Wroclaw II Infectious Diseases Ward 51-149 Wrocław POLAND
Site No. 0605 Voivodeship Hospital Observational and Infectious Diseases Ward T. Chałubińskiego 7 75-581 Koszalin POLAND	
Site No. 0701 FNsP F. D. Roosevelta Banska Bystrica Infectology department Nám. L. Svobodu 1 975 17 Banská Bystrica SLOVAKIA	Site No. 0702 General Hospital Lucenec Infectology department Namestie republiky 15 984 39 Lucenec SLOVAKIA
Site No. 0704 University Hospital Presov Department of transmissible diseases Holleho 14/A 080 01 Presov SLOVAKIA	Site No. 0705 NsP Zilina Department of internal medicine ul.Vojtecha Spanyola 43 012 07 Zilina SLOVAKIA
Site No. 0901 Consorcio del MARESME - H MATARÓ Cuidados Intensivos Carretera de Cirera s/n 08304 MATARÓ SPAIN	Site No. 0902 Hospital Universitario de Torrejón Servicio de Medicina Interna C /Mateo Inurria, s/n 28850 Torrejón de Ardoz SPAIN
Site No. 0903 Hospital Germans Trias i Pujol	Site No. 0904 Hospital Clinic of Barcelona

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Enfermedades Infecciosas Infectious Diseases Carretera de Canyet s/n. 08916 Badalona SPAIN	C/ Villarroel 170, Sala de Neunología, Escalera 6, Planta 2 08036 Barcelona SPAIN
Site No. 0905 Hospital Universitario de la Princesa Neumologia c/ Diego de León 62 28006 Madrid SPAIN	Site No. 0906 Hospital Universitario Puerta de Hierro Internal Medicine Manuel de Falla 1 28222 Majadahonda SPAIN
Site No. 0907 Hospital del Mar Doctor Aiguader, 88 08003 Barcelona SPAIN	Site No. 0908 Hospital Universitario La Paz Urgencias Paseo de la Castellana 261, 28046 Madrid SPAIN
Site No. 1001 Institutul national de boli infectioase “Prof. Dr. Matei Bals” Str. Dr. Calistrat Grozovici, nr. 1, Sector 2 021105 Bucharest ROMANIA	Site No. 1002 Spitalul Clinic de Boli Infectioase si Tropicale “Dr. Victor Babes” Soseaua Mihai Bravu Nr. 281,Sector 3 030303 Bucharest ROMANIA
Site No. 1003 Spitalul Clinic de Boli Infectioase Constanta Bulevardul Ferdinand, Nr. 100 900708 Constanta ROMANIA	Site No. 1004 Spitalul Clinic de Boli Infectioase si Pneumoftiziologie “Dr. Victor Babes” Str. Gheorghe Adam Nr. 13 300310 Timisoara ROMANIA
Site No. 1005 Spitalul Clinic De Boli Infectioase “Sfanta Parascheva” Str. Octav Botez, Nr.2 700116 Iasi ROMANIA	Site No. 1006 Spitalul de boli infectioase Brasov Str. Mihai Viteazu, Nr.9 500174 Brasov ROMANIA
Site No. 1007 Spitalul Judetean de Urgenta “Sf. Ioan Cel Nou” Bulevardul 1 Decembrie 1918, Nr.21 720237 Suceava ROMANIA	Site No. 1008 Spitalul Clinic de Boli Infectioase si Pneumoftiziologie “Dr. Victor Babes” Str. Calea Bucuresti, Nr. 126 200515 Craiova

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	ROMANIA
Site No. 1009 Spitalul clinic de boli infectioase Cluj Napoca Strada Iuliu Moldovan, Nr.23 400348 Cluj ROMANIA	Site No. 1010 Spitalul Clinic Județean de Urgență Sibiu Bulevardul Coposu, Nr 2-4, 550245 Sibiu ROMANIA
Site No. 1101 Vidzemes hospital Jurmalas street 195 LV-4201 Valmiera LATVIA	Site No. 1102 P.Stradins Clinical university hospital Pilsonu street 13 LV-1002 Riga LATVIA
Site No. 1103 Ziemelkurzemes Regional hospital Ltd Inzenieru street 60 LV-3601 Ventspils LATVIA	Site No. 1104 Liepaja's Regional hospital Slimnicas street 25 LV-3414 Liepaja LATVIA
Site No. 1105 Rezeknes hospital 18 Novembra street LV-4600 Rezekne LATVIA	
Site No. 1204 Infekciniu ligu centras Infekciniu ligu ir tuberkuliozes ligonine, VsI VULSK filia Birutes gatve 1 08117 Vilnius LITHUANIA	
Site No. 1301 Pneumonology Department Specialized Hospital for Active Treatment of Pneumo-Physiatric Diseases D-r Dimitar Gramatikov - Ruse, EOOD 1 Aleya Liliya Str. 7000 Ruse BULGARIA	Site No. 1304 Department Internal Diseases Multiprofile Hospital for Active Treatment Sveti Pantaleimon-Pleven, Pleven OOD Druzhba Qtrs, 24 Trite Bora Str. 5800 Pleven BULGARIA
Site No. 1305 Department of Pulmonology and Phtysiatry	Site No. 1306 Department - Internal Diseases

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<tr><td colspan="2">Multiprofile Hospital for Active Treatment
1 Hristo Botev Str.
8800 Sliven
BULGARIA</td><td>Multiprofile Hospital for Active Treatment
1 Dr. Iliev Detskiya Str.
5300 Gabrovo
BULGARIA</td></tr>
<tr><td colspan="2">Site No. 1307
Department Infectious Diseases
Multiprofile District Hospital for Active Treatment Dr Stefan Cherkezov, AD
1 Nish Str.
5000 Veliko Tarnovo
BULGARIA</td><td></td></tr>
<tr><td colspan="3">Publication (reference):
Results of study not yet published</td></tr>
<tr><td>Study period (years):
2.5 years</td><td>Date of first enrolment:
January 26th, 2013
Date of last completed
May 15th, 2015</td><td>Phase of development:
Phase II, Proof of Concept
Dose Finding</td></tr>
</table>

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Objectives:

The objectives were to evaluate the efficacy and safety of inhaled LASAG (three times daily) plus standard of care in the treatment of patients with indication for hospitalization due to acute serious influenza OR an influenza caused worsening of a primary medical condition in comparison with placebo inhalation three times daily plus standard of care.

Primary objective:

To evaluate the clinical efficacy of inhaled 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 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.

1) effects on time to return to work, school or usual level of functioning
2) effects on secondary pneumonia and other bacterial infections
3) effects on occurrence of bronchospasms during inhalation

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Secondary objectives:

1) To evaluate the clinical efficacy of inhaled 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 as measured by
   a) time to alleviation of clinical influenza signs.
      Clinical Influenza Signs and Resolution Criteria are defined as:
      1. Body Temperature
         - ≤ 37.2 °C (≤ 99 °F) oral
         - ≤ 37.8°C (≤ 100°F) rectal or tympanic

         NOTE: Axillary measurement is prohibited
      2. Oxygen saturation
         - ≥ 92% (without oxygen feed)
      3. Respiratory rate
         - ≤ 24/minute
      4. Heart rate
         - ≤ 100/minute
      5. Systolic BP
         - ≥ 90 mm Hg

      Time to alleviation was defined as the time in hours from first inhalation of LASAG until resolution of at least 4 of the 5 clinical signs described above within the defined resolution criteria shown and maintained for at least 24±2 hours without use of symptomatic relief medication (i.e. acetaminophen). 2 of the 4 resolution criteria had to be body temperature and oxygen saturation.
   b) routine daily activity score on functional visual analog 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).
2) To evaluate the antiviral efficacy, as measured by duration and level of viral shedding, of inhaled LASAG plus standard of care compared to placebo plus standard of care in patients hospitalized with acute serious influenza OR an influenza caused worsening of a primary medical condition
3) To evaluate the safety and tolerability of inhaled LASAG in patients hospitalized with acute serious influenza OR an influenza caused worsening of a primary medical condition.
4) To assess effect of LASAG on influenza related and all-cause mortality at follow-up visit 3

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Explorative objectives:

1) To assess effect of LASAG on rates of ICU admission, need for ventilator support and supplemental oxygen requirements
2) To assess effect of LASAG on length of hospital stay above 5 days
3) To assess effect of LASAG on time to return to work, school or usual level of functioning
4) To assess effect of LASAG on secondary pneumonia and other bacterial infections
5) To assess effect on LASAG on occurrence of bronchospasms during inhalation

Methodology:

Screening and randomization

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 laboratory confirmation prior to randomization using RT-PCR or an approved rapid antigen test.

Treatment Phase

Subjects were hospitalized and had a daily investigator's visit (preferably between 12:00-14:00) to perform a physical examination, and to inquire concomitant medications and adverse events. Subjects received 15 doses of study medication by AKITA JET nebulizer on 5 to 6 consecutive days. Prior to each inhalation vital signs, oxygen requirements and O_2 saturation, concomitant medications, adverse events and a symptom questionnaire are recorded. Repeated safety labs were obtained prior to the 8^{th} dose, and on follow-up visit 1. Nasal and throat swabs were obtained prior to the 8^{th} dose. Recording of influenza relief medication (i.e. acetaminophen) administered since completion of the last symptom questionnaire

Follow-up

All subjects had 3 similar follow-up visits at dedicated time points 2, 9, 23 days after treatment termination. In addition, safety labs were repeated at follow-up visit 1 and a urine pregnancy test was repeated at follow-up visit 2.

Subjects remaining in hospital after end of treatment passed daily visits to record symptom questionnaire, vital signs, O_2 saturation and requirements three times daily, and physical examination, concomitant medications, adverse events, weight, ECG and X-Ray results, if applicable, once daily.

End of study

After end of study all patients continued to be treated according to the standard of care procedures of the involved hospitals if still necessary in the Investigator's opinion.

<table>
<tr><td>Name of Sponsor/Company:
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Germany</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

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Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
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LASAG for inhalation</td></tr>
<tr><td>Name of Active Ingredient:
ASA (800mg fill dose is equivalent to 400 mg ASA/4 mL fill dose)</td></tr>
<tr><td colspan="3">Number of patients (planned and analyzed):
planned: 200 (140 evaluable for primary analysis)
screened: 171
randomized: 115
Main analysis of efficacy reported here
evaluable: 81 (MITT population)
The initially applied low dose of LASAG (400 mg LASAG/4mL fill dose equivalent to 200 mg/4mL ASA fill dose) (only 6 patients) according to the initial clinical study protocol V2.2 (19 Oct 12) and the patients without positive influenza test (26 patients) were reported separately.</td></tr>
<tr><td colspan="3">Diagnosis:
Patients with indication for hospitalization due to acute serious influenza (not subject to admission to Intensive Care Unit (ICU) due to breathing instability and able to breathe from a nebulizer) OR an influenza caused worsening of a primary medical condition.</td></tr>
</table>

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Main criteria for inclusion were:

1) Age ≥ 18 and ≤ 80 years
2) Ability to provide written informed consent prior to performance of any study-related procedure
3) Ability to perform controlled inhalations with the AKITA JET device according to the investigator's opinion
4) Indication for hospitalization due to suspected acute severe influenza OR patients with another medical condition (e.g. diabetes mellitus, COPD or other chronic lung disease) worsened by influenza and leading to indication for hospitalization
5) Living in a community with documented current influenza transmission, confirmed by viral culture or RT-PCR *OR* patients with influenza like illness with positive rapid antigen test or RT-PCR at screening
6) Presence of at least one respiratory symptom (nasal congestion, sore throat or cough) of any severity (mild, moderate, or severe) and present admission to hospital due to (suspected) influenza
7) Presence of at least one constitutional symptom (aches/myalgia, fatigue headache or feverishness/chills/sweat) of any severity (mild, moderate, or severe) and present admission to hospital due to (suspected) influenza
8) Presence of fever at time of screening of ≥ 38.0 °C taken orally, or ≥ 38.5 °C taken rectally or tympanic OR history of documented fever or patient reported symptom of feverishness at any time during 48 hours prior to screening
9) Patient reported onset of illness less than 120 hours (=5 days) before first study drug application
10) Female participants of childbearing (reproductive) potential must have a negative urine pregnancy test at screening and agree to use an acceptable method of contraception throughout their participation in the study. Acceptable methods of contraception (a Pearl Index < 1%) include:
    - hormonal methods (oral contraceptives, patches or medroxyprogesterone acetate)
    - An intrauterine device (IUD) with a documented failure rate of less than 1% per year
    - Abstinence may be considered an acceptable method of contraception at the discretion of the investigator

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Main criteria for exclusion were:

1) Current clinical evidence or suspicion of an acute non-influenza infectious illness at the time of screening and baseline visit
2) Subjects who have been hospitalized due to a condition other than acute influenza and in whom influenza is diagnosed during hospitalization
3) Known allergy or hypersensitivity against Acetylsalicylic Acid (ASA) or LASAG
4) ASA induced asthma or patients with insufficiently controlled bronchial asthma
5) Presence of any chronic lung condition requiring either continuous or intermittent oxygen therapy
6) Requirement for acute or chronic mechanical ventilation, either via oral or nasotracheal intubation or via tracheostomy, or chronic or intermittent requirement for BiPAP (bilevel positive airway pressure) at screening
7) Respiratory instability requiring ICU admission resulting in inability to breathe from a nebulizer
8) Immunized against influenza with live attenuated virus vaccine in the previous 4 weeks (=4x7 = 28 days)
9) Presence of one of the following uncontrolled or unstable cardiovascular diseases: stroke, ECG confirmed acute ischemia or myocardial infarction and/or clinically significant dysrhythmia
10) Presence of cardiac signs or symptoms compatible with NYHA Class IV functional status for congestive heart failure
11) Known history of gastrointestinal bleeding, uncontrolled peptic or uncontrolled duodenal ulcer
12) Known history of moderate or severe renal impairment and/or previous clinical laboratory data indicating an estimated creatinine clearance <30 mL/min during the last 12 months (=12x28 days = 336 days)
13) Known history of clinically significant proteinuria ($\geq$ 1000 mg/24 hrs) during the last 12 months (=12x28 days = 336 days)
14) Presence of currently uncontrolled hyperuricaemia and/or diminished excretion of uric acid without appropriate pharmacotherapy during the last 12 months (=12x28 days = 336 days)
15) Known history of unstable cirrhosis or unstable advanced liver disease (Child-Pugh class B or C)
16) Known history of hemophilia or other bleeding disorders
17) History of organ transplantation, congenital immunodeficiency
18) Use of immunosuppressive therapies with a 10mg or more prednisolone-equivalent dose during the last 6 months (=6x28 days = 168 days). Use of inhaled glucocorticoids is permitted
19) Known history of human immunodeficiency virus (HIV) infection
20) Patients currently on or likely to require anticoagulation with coumarin, heparin, warfarin or similar products
21) Expected explicit need for NSAIDs (non-steroidal anti-inflammatory drugs) during the study that cannot be covered by symptomatic acetaminophen (i.e. paracetamol) therapy (e.g. patients with chronic rheumatic conditions)
22) Presence of any cancer type (hematologic or solid tumor), that requires chemotherapy or radiation therapy, with the exception of localized non-melanoma skin cancer

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ASA (800mg fill dose is equivalent to 400 mg ASA/4 mL fill dose)</td><td>Page:</td></tr>
<tr><td colspan="3">23) Known history of alcohol abuse or drug addiction during the last 12 months (=12x28 days = 336 days)
24) Presence of a psychiatric illness or dementia that would preclude ability to use a nebulizer or complete the symptom questionnaire
25) Use of intravenous or intramuscular medications, containing acetylsalicylic acid within 72 hours prior first LASAG inhalation
26) Participation in a clinical study using an experimental medication during the last 4 weeks (=4x7 days = 28 days)
27) Women who are pregnant, breast-feeding or who are willing to become pregnant during the course of the study
28) Vulnerable patients who are not able to give informed consent or who might depend on the clinical study site or investigator</td></tr>
<tr><td colspan="2">Test product, dose and mode of administration:
LASAG group: 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.</td><td>batch number:
IMP collection batch number:
001 MUL, 002 MUL, 003 MUL, 004 MUL</td></tr>
<tr><td>Duration of treatment:
15 inhalations on 5 to 6 consecutive days</td><td>Divided into following phases:
1. Screening
2. Baseline
3. Treatment:
15 inhalations on 5 to 6 consecutive days
4. Follow-up</td><td>Follow-up:
Follow-up visit 1:
02 days after end of treatment
Follow-up visit 2:
09 ±2days after end of treatment
Follow-up visit 3:
23±2 days after end of treatment</td></tr>
<tr><td colspan="2">Reference therapy, dose and mode of administration:
Placebo group: 4 mL saline solution (0.9% Sodium chloride (NaCl)).</td><td>batch number:
IMP collection batch number:
001 MUL, 002 MUL, 003 MUL, 004 MUL</td></tr>
</table>

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CRITERIA FOR EVALUATION:

Efficacy:

Primary variable

Time to alleviation of clinical influenza symptoms 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. Influenza symptoms were nasal congestion, sore throat, cough, aches/myalgia, fatigue, headaches, feverishness/chills/sweats. Symptoms were documented on a symptom questionnaire.

Secondary variables

1) Time from start of treatment to alleviation of at least 4 of 5 clinical influenza signs maintained for at least 24±2 hours and without use of symptomatic relief medicines (i.e. acetaminophen)
2) Percentage of subjects whose influenza symptoms have completely resolved at specific time points (after inhalations 5, 8, 11 and 14)
3) Percentage of subjects whose influenza signs have completely resolved at specific time points (after inhalations 5, 8, 11 and 14)
4) Composite symptom score changes over time (AUC)
5) Change in viral load before inhalation 8
6) Percentage of subjects with >2-log drop in viral load prior to 8^{th} dose
7) Descriptive statistics regarding adverse events and treatment discontinuations
8) Descriptive statistics of influenza related and all-cause mortality at follow-up visit 3

Exploratory criteria / variables

1) Percentage of subjects requiring ICU admission and/or intubation, median number of ICU and/or ventilator days
2) Proportion of subjects with O2 saturation <93% requiring supplemental oxygen at specified time points and median time to no need for supplemental O2
3) Median length of hospital stay above 5 days
4) Descriptive statistics regarding bacterial complications of influenza
5) Percentage of subjects requiring short-acting beta-agonists (e.g. Salbutamol) to manage bronchospasms

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Safety:

1) Treatment emergent adverse events
2) Symptoms of airway reactivity
3) Pharyngeal symptoms
4) Physical examinations and vital signs
5) Clinical laboratory assessments (hematology, biochemistry, blood clotting)

STATISTICAL METHODS:

General remark

The statistical analysis used deductive tests for the primary analysis, explorative tests for the secondary analysis and descriptive methods for the remaining analyses, the level of significance was 5%. The primary analysis used 2.5% for a one-sided-test. The primary analysis was computed using blinded data.

Populations of Analysis

Primary efficacy analysis:

Modified intent-to-treat (MITT) consisting of all subjects randomized in the trial who received at least one dose of study drug (or an inhalation of placebo) and who had influenza infection confirmed by RT-PCR.

Per Protocol Analysis:

The per protocol (PP) set included all MITT subjects with at least 13 inhalations and no major protocol deviations (identified prior to database lock and unblinding).

Safety analysis:

The safety set (SS) consisted of all patients randomized in the trial who received at least one dose of study drug.

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SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

The primary analysis did not result in a significant difference between both treatment groups (log rank test of p=0.35 in favor of placebo). Sensitivity analyses using different allocations of treatment groups and two different per protocol populations as well as the follow-up analysis were not contradicting this result.

Secondary results of efficacy presented interesting trends for better LASAG results in the full MITT. These trends did not yield significant results however. Alleviation time of clinical signs was shorter for LASAG (26.6 hours versus 33.6 hours, p=0.10 in favor of LASAG). The composite symptom score decreased a bit more pronounced (median -8.7 versus -7.8, p=0.78) in the LASAG group and the daily activity score improvement of LASAG was superior to that of placebo (3.2 versus 2.7, p=0.25).

In addition to these results for MITT population, supporting sub analyses provided a better insight into the factors influencing the result. These additional analyses were of explorative nature and may help to interpret the primary outcome. The main result of these analyses supported the apriori hypothesis of an interaction of treatment and the baseline composite symptom score (CSS). Patients suffering from high symptom scores (CSS≥17) at baseline showed a significantly lower time to alleviation of symptoms if treated with LASAG compared to placebo (LASAG 44.7 ± 16.2 h vs. placebo 71.5 ± 34.5 h; log rank test p=0.0229). Thus, a statistically significant and clinically meaningful reduction in the time to alleviation of Influenza symptoms could be demonstrated in patients showing relevant symptoms at baseline. These results are in line with the a priori hypothesis that an effect of treatment with LASAG can best be seen in patients with relevant symptoms. At the same time the overall results clearly show the limitations of patient reported outcomes as a primary endpoint: significant results could only be obtained in very symptomatic patients, although also patients with less symptoms might benefit from LASAG therapy.

SAFETY RESULTS:

Adverse event rates were similar (LASAG: 41 AEs affecting 23 patients; placebo: 42 AEs affecting 21patients). Grading, treatment and outcome of AEs were similar. A total of 10 AEs were categorized as treatment related in the LASAG group (24% of AEs) compared to 4 (10%) in the placebo group. The great majority of these LASAG TRAEs were airway related (n=7 or 70%) but none of the placebo TRAEs were airway related. AEs resulting in discontinuation of treatment occurred in the LASAG group only (7 AEs, 6 patients affected).

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CONCLUSION:

The primary analysis did not yield significant results. Time to alleviation of symptoms was slightly lower in the placebo group but this did not achieve statistical significance. Sensitivity analyses as well as follow-up analysis concurred with this result. The secondary analysis also showed no significant results but trends in favor of LASAG. Both treatments provided similar frequencies of AEs, while TEAEs and discontinuation as result of AEs were (not significantly) more frequent in the LASAG group.

There was some evidence that the population of patients was not optimal as many patients were included in a state where the influenza symptoms were already declining or were not very pronounced anymore, so that they presented alleviated symptoms after a very short time period even under placebo treatment. Measurable effects of LASAG inhalation applied with the AKITA Jet are more or less restricted to patients with high symptom scores at baseline, as shown by additional post hoc analyses based on background a priori hypotheses that patients with more severe symptoms will receive additional benefit..

Date of the report:

April, 11th, 2016