A Prospective, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of BAY 41-6551 as Adjunctive Therapy in Intubated and Mechanically-Ventilated Patients with Gram-Negative Pneumonia

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To evaluate the efficacy (superiority) and safety of BAY 41-6551 as measured by the comparison of the clinical cure rate of aerosolized BAY 41-6551, administered via the PDDS Clinical, versus placebo (normal saline) at the Test-of-Cure (TOC0 visit...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON44738

Source
ToetsingOnline

Brief title
BAY 41-6551 in Intubated and Mechanically-Ventilated Pneumonia Patients

Condition

- Bacterial infectious disorders
- Respiratory tract infections

Synonym
Gram-negative Pneumonia

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Bayer AG

Intervention

Keyword: BAY 41-6551, Efficacy, Gram-Negative Pneumonia, Safety

Outcome measures

Primary outcome

Efficacy variables:

The primary efficacy variable will be the clinical response at the Test-of-Cure (TOC) visit in the modified Intent-to-Treat (mITT; ie, ITT population plus a pre-therapy culture positive for a Gram negative respiratory tract pathogen and an APACHE II score of * 10) population. The mITT population will be the primary analysis group.

Safety variables:

All patients who have received at least one dose of the study drug(s) will be evaluated for safety in a descriptive manner. The safety analysis will include tabulation of the type (using Medical Dictionary for Regulatory Activities [MedDRA] glossary) and frequency of all AEs. Drug-related AEs, serious AEs (SAEs), and premature discontinuations due to AEs will also be summarized, as well as AEs by severity, outcome, and action taken.
Incidence tables will be presented for all AEs up to seven days after the end of treatment and for SAEs up to Day 28 visit.

All laboratory data will be analyzed using descriptive statistics including identification of laboratory data outside normal ranges.

Rates of organ failure will also be summarized by patient as well as by specific organ type.

Mortality during the treatment period, Day 15 and Day 28 visit will be summarized.

Secondary outcome

The secondary objectives are to evaluate the efficacy of BAY 41-6551 (versus placebo) as measured by:

* The number of days on mechanical ventilation

* The number of ICU days at Day 28

* The total number of days of Gram-negative intravenous (IV) antibiotics per patient

* CPIS changes through TOC

* The clinical relapse rates at Day 28

* The all all-cause mortality rate during therapy, at Day 15, and at Day 28

* The number of hospital days at Day 28

Secondary microbiological objectives will include comparisons (aerosolized BAY 41-6551 versus placebo) of the:

* per pathogen microbiological response rates at the TOC visit

* per patient microbiological response rate at the TOC visit

* microbiological recurrence rates at the TOC and Day 28 visit

* emergence of new respiratory pathogens during the treatment period

* emergence of resistance among baseline pathogens in those patients with

persistent infection or colonization

Study description

Background summary

Amikacin is a semi-synthetic aminoglycoside antibiotic derived from kanamycin A with demonstrated in vitro activity against aerobic Gram-negative bacteria, particularly those with increased resistance associated with hospital-acquired infections. It is used intravenously
(IV) or intramuscularly (IM) for the treatment of infections caused by Gram-negative microorganisms.
Aerosolized delivery of amikacin inhalation solution offers an attractive adjunctive therapeutic option to systemic to IV or IM treatment of lower respiratory tract infections because it minimizes systemic exposure while delivering amikacin directly to the site of infection.
Aerosolized antibiotics have been administered as adjunctive therapy tomechanically-ventilated patients with deep lung infections, specifically including hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and ventilator-associated tracheobronchitis. Efforts to improve therapies of inhalation antibiotics have been hampered by the low efficiency of pulmonary drug delivery with conventional nebulizers connected to ventilator circuits.

Study objective

To evaluate the efficacy (superiority) and safety of BAY 41-6551 as measured by the comparison of the clinical cure rate of aerosolized BAY 41-6551, administered via the PDDS Clinical, versus placebo (normal saline) at the Test-of-Cure (TOC0 visit in patients with microbiologically confirmed Gram negative pneumonia.

Study design

This is a prospective, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of 10 calendar day (20 doses) course of aerosolized BAY 41-6551 400 mg (amikacin as free base) every 12 hours versus placebo (normal saline) as adjunctive therapy in intubated and mechanically-ventilated patients with Gram negative pneumonia. All patients will receive parenteral antibiotics according to the 2005 ATS/IDSA guidelines for the management of HAP, VAP, or HCAP for 10 days. Patients who are extubated before completing the full course (10 calendar days if the first dose is

administered in the AM or 11 calendar days if the first dose is administered in the PM [20 doses]) of aerosol therapy will be continued on aerosolized therapy with the handheld adaptor.
Seven to ten days after completing 10 days of aerosolized treatment, patients will be evaluated for clinical response, which will be assessed based on the results of chest x-rays, CPIS scores, use of antibiotic therapy, and survival.

Intervention

Aerosolized BAY 41-6551/placebo is given via the Pulmonary Drug Delivery System [PDDS Clinical] to Intubated and Mechanically Ventilated Patients with Gram Negative Pneumonia as Adjunctive Therapy to the Standard of care antimicrobial treatment as per the 2005 American Thoracic Society (ATS) / Infectious Diseases Society of America (IDSA) Guidelines for the Management of Hospital-Acquired Pneumonia (HAP), Ventilator-Associated Pneumonia (VAP), or Healthcare-Associated Pneumonia (HCAP)

Study burden and risks

Following examinations will be performed:
- Brief Physical Exam/Vitals: 10x Treatment Visit (i.e. Day1 until Day 10) temperatuur), lengte en gewicht: 10x Treatment Visit (i.e. Dag 1 tot Dag 10)
- Assessment of clinical signs and symptoms of pneumonia: 1X at Screening, 10x Treatment Visit (i.e. Day1 until Day 10), 1X Premature Discontinuation Visit, 1X Test of Cure (TOC) Visit, 1X Late FU Visit
- Chest X-Ray: 1X at Screening, 1X Day 1, 1X Day 3, 1X Day 5, 1X Day 7, 1X Day 10 (End of Treatment Visit), 1X Premature Discontinuation Visit, 1X Test of Cure Visit, 1X Late FU Visit

With chest x-rays, there is no discomfort, but the patient will be exposed to a very low level of radiation with risks as seen for routine practice.

- Urine or Serum pregnancy test: 1X at Screening
- Hematology / Serum Chemistry / Urinalysis: 1X at Screening, 1X Day 1, 1X Day 3, 1X Day 5, 1X Day 7, 1X Day 10 (End of Treatment Visit), 1X Premature Discontinuation Visit, 1X Test of Cure (TOC) Visit, 1X Late FU Visit
- Aerobic blood culture: 1X at Screening (if the result is positive, to be repeated as needed , Days 1, 3, 5, 7, 10, Test of Cure Visit, Late FU Visit, until negative)
- Arterial blood gases/pulse oximetry: 1X at Screening, 1X Day 1, 1X Day 3, 1X Day 5, 1X Day 7, 1X Day 10 (End of Treatment Visit), 1X Premature Discontinuation Visit, 1X Test of Cure (TOC) Visit, 1X Late FU Visit
- Serum creatinine: 10x Treatment Visit (i.e. Day1 until Day 10)
- Serum amikacin trough level: 10x Treatment Visit (i.e. Day1 until Day 10)

Possible side effects for collection of blood: discomfort, pain, bleeding,

burning, dizziness, fainting or bruising at the site where blood is drawn. There is also a slight risk of local infection. The total amount of blood that will be taken on any study day is about 25 mL. The maximum amount of blood that will be taken over the entire study is about 220-230 mL.

- Collect respiratory specimen for Gram stain and culture: 1X at Screening, 1X Day 1, 1X Day 3, 1X Day 5, 1X Day 7, 1X Day 10 (End of Treatment Visit), 1X Premature Discontinuation Visit, 1X Test of Cure (TOC) Visit, 1X Late FU Visit
- Pleural fluid culture: 1X at Screening (if the result is positive, to be repeated as needed , Days 1, 3, 5, 7, 10, Test of Cure Visit, Late FU Visit, until negative)
- Study Medication: 10x Treatment Visit (i.e. Day1 until Day 10), doses every 12 hours, therefore 20 doses in total

Very little is known about the risks of amikacin as an aerosol as amikacin has not been given to patients very often in this way. What is known are the type of side effects that amikacin may have when given in the usual way, intravenous or intramuscular.
When given through a needle into a patient*s muscle or vein, amikacin has caused side effects that may include rash, fever, headache, tingling, tremor, nausea, vomiting, eosinophilia, joint aches, anemia, and low blood pressure. In addition, serious side effects that may occur include nephrotoxicity and ototoxicity, and neurotoxicity, paresthesias and dysesthesias. Hearing problems may occur after the treatment with amikacin has stopped. In the case of hearing loss, this side effect could be permanent. Systemic administration of amikacin can also lead to neuromuscular blockade and respiratory paralysis in rare cases. Neuromuscular blockade causes paralysis of the skeletal muscles. It is more likely in patients who also receive anesthetics and neuromuscular blocking agents. The concurrent use of amikacin with potent diuretics: ethacrynic acid or furosemide should be avoided since diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may increase ototoxicity of amikacin.

Over 100 patients and healthy volunteers have had the inhaled form of amikacin via the PDDS Clinical delivery system in 4 clinical trials. The inhaled amikacin was well tolerated in these individuals and the risks associated were low. Possible reactions to this method of giving the drug is bronchospasm and worsening of kidney function.

As with any medication, there is always a risk, however small, of severe allergic reaction, which may occur within 24 hours of taking the medication and can include severe itching, difficulty breathing, and respiratory failure that can result in death. When a medication is given directly into the lung, there is a chance that it could lead to irritation of the upper airways and the lung, with coughing or wheezing and/or breathing problems as a result.

- Late Follow-up Questionnaire: 1X Late FU Visit

Please note that the questionnaire as described in the Protocol section 15.6 is reported in the CRF and questions are going to be completed directly into the CRF by the investigator during the Late Follow-Up face to face or phone call with the patient. This questionnaire is a guidance for the Investigator to help the him/her on collecting all the relevant data from the patient during the Late Follow-Up visit/call. The patient will not complete this questionnaire directly.

Contacts

Public
Bayer

Kaiser-Wilhelm-Allee 51368
Leverkussen 51368
DE
Scientific
Bayer

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Leverkussen 51368
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients of age 18 and older, who are hospitalized, have pneumonia suspected or confirmed to be caused by Gram-negative organisms, and who are intubated and mechanically-ventilated will be selected for this study. In all patients where the pathogen is suspected of

being Gram-negative, it should be confirmed as soon as culture results are available. Patients with microbiologically-confirmed pneumonia are those who have a Gram-negative organism cultured from an appropriate respiratory tract specimen collected prior to enrollment. The main inclusion criteria are:
*
Males and non-pregnant, non-lactating females, 18 years of age or older
Intubated and mechanically-ventilated
Diagnosis of pneumonia defined as presence of a new or progressive infiltrate(s) on chest radiograph
Presence of Gram-negative organism(s) indicated by Gramstain, or culture of pre-therapy respiratory specimen, or suspected Gram-negative pathogen
Impaired oxygenation
Clinical Pulmonary Infection Score (CPIS) * 6
The presence of a MDR organism in a pre-therapy respiratory
specimen OR at least two risk factors for MDR organisms

Exclusion criteria

The main exclusion criteria are:
* A history of hypersensitivity to amikacin, or other
aminoglycosides,
* Has received systemic Gram-negative antibiotic therapy for greater than 48 hours at the time of administration of first dose of study drug. There should be as minimal a time delay as possible between randomization and first dose of study drug but up to 48 hours will be acceptable.
Exception: Systemic antibiotic therapy for more than 48 hours for gram-negative infection prior to administration of first dose of study drug is permitted if the infection is caused by pathogens that are resistant to the antimicrobial agent(s) used, or the patient*s pneumonia is worsening.
* Has primary lung cancer (including patients with small cell lung carcinoma/non-small cell lung carcinoma and patients with unknown histology) or another malignancy metastatic to the lungs or other known endobronchial obstructions.
Exception: Please note that patients with complete resection of non-small cell lung carcinoma are eligible for the study.
* Known or suspected active tuberculosis, cystic fibrosis, human immunodeficiency virus (HIV) infection with CD 4 count
200 cell/mm3, or invasive fungal infection of the lung, lung abscess, or empyema
* Known or suspected bacteremia secondary to Staphylococcus
aureus
* Known or suspected neuromuscular disorders such as myasthenia gravis or parkinsonism
* Has had a stroke within five days
* A positive urine and/or serum beta-human chorionic gonadotropin (*-hCG) pregnancy test
* Burns greater than 40% of total body surface area
* Patients with a serum creatinine * 2 mg/dL (177 *mol/L)
Exception: Patients with a serum creatinine * 2 mg/dL (177 *mol/L) and being treated with

continuous renal replacement therapy (continuous veno-venous hemofiltration [CVVH] and continuous veno-venous hemofiltration with dialysis[CVVH-D]) or daily hemodialysis will receive the
aerosol study drug treatment (Section 8.4.6.1)
* Neutropenia (Screening absolute neutrophil count [ANC] * 103 neutrophils/mm3)
* Has been on mechanical ventilation for * 28 days
* Is participating in or has participated in other investigational interventional studies within the last 28 days prior to study treatment
* The risk of rapidly fatal illness and death within 72 hours, or any concomitant conditions not related to VAP that, in the opinion of the investigator, precludes completion of study evaluations and the course of therapy
* Stem cell transplantation
* Patients with documented Legionella infection (eg, Legionella pneumonia)
* Has an Acute Physiology and Chronic Health Evaluation II (APACHE II) score < 10
* Patients receiving veno-venous extracorporeal circulation membrane oxygenation (V-V ECMO)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-06-2014
Enrollment:	9
Type:	Actual

Medical products/devices used

Generic name:	Pulmonary Drug Delivery System (PDDS)

Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	Niet van toepassing
Generic name:	Amikacin Sulfate 1:1.8 Solution for Inhalation

Ethics review

Approved WMO Date:	28-03-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-03-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-08-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-01-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-03-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-11-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	26-07-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-08-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-10-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-11-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-10-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-11-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-000906-35-NL
CCMO	NL43977.091.13