Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Date of study report:	29 MAY 2008
Study title:	An Open-Label, Multicenter, Multinational Study to Assess the Safety, Tolerability and Pharmacokinetics of Aerosolized Amikacin Delivered via the Pulmonary Drug Delivery System (NKTR-061) in Intubated and Mechanically-Ventilated Patients with Nosocomial Pneumonia
Sponsor's study number:	06-IN-AK004
NCT number:	NCT01021436
EudraCT number:	2006-005079-17
Sponsor:	Bayer HealthCare
Clinical phase:	Phase II
Study objectives:	Primary objective: To determine the pharmacokinetic (PK) profile of aerosolized amikacin administered via the Pulmonary Drug Delivery System (PDDS) clinical device (NKTR-061) in subjects with nosocomial pneumonia caused by gram-negative organisms Secondary objective: To evaluate the safety and tolerability of aerosolized amikacin administered via the PDDS clinical device in subjects with nosocomial pneumonia caused by gram-negative organisms
Test drug:	Amikacin inhalation solution (BAY 41-6551)
Name of active ingredient(s):	Amikacin sulfate
Dose:	125 mg/mL as a nominal dose of 400 mg every 12 h
Route of administration:	Inhalation/aerosol
Duration of treatment:	For 7-14 days
Reference drug:	Not applicable
Indication:	Pneumonia
Diagnosis and main criteria for inclusion:	• Males or female subjects 18 years of age or older with confirmed pneumonia, defined as the presence of a new or progressive infiltrate(s) on chest radiograph and the presence of gram-negative organism by either culture or Gram stain of respiratory secretion, were eligible for enrollment. The subjects must have been intubated and mechanically ventilated and expected to remain so for at least 3 days after the start of study treatment. Subjects with a tracheostomy were also eligible.
Study design:	The study was conducted in an open-label, multicenter, multinational design.

Methodology:	The study consisted of a 1- to 2-day screening period followed by a 7- to 14-day treatment period and a follow-up visit 28 days after the administration of the first treatment dose. Subjects received aerosolized amikacin via the PDDS clinical device (NKTR-061) placed in a ventilator circuit (when the subject was intubated and mechanically ventilated) or handheld (when the subject had been extubated and removed from mechanical ventilation). Nebulization of the dose was to be completed in approximately 45-60 min in intubated subjects and in approximately 15-20 min in extubated subjects. Doses were to be modified for subjects with renal insufficiency indicated by elevated serum creatinine levels and for evidence of bronchospasm during dosing. Safety was monitored throughout the study. Blood samples for PK were obtained before dosing and up to 12 h post-dose after the start of dosing. Blood samples were obtained at 1 h and 12 h after the administration of the second dose (ie, 13 and 24 h after the first dose). Two urine samples were obtained on Day 3 at the start of dose and up to 12 h after both first and second dose. Tracheal aspirates obtained on Day 3 as part of the subject's standard care were quantitatively collected. Each sample obtained was measured for volume and analyzed for amikacin concentration. Approximately 15-30 min after completion of the morning dose of study medication on Day 3, a standard bronchoscopic procedure was performed with bronchoalveolar lavage (BAL) fluid collection from the pneumonic area of the lung. Each BAL fluid sample was analyzed for amikacin concentration which was expressed as epithelial lining fluid (ELF) concentration using the urea dilution method.
Study center(s):	The study was conducted at four centers in USA and two centers in France.
Publication(s) based on the study (references):	Luyt CE, Clavel M, Guntupalli K, Johannigman J, Kennedy JI, Wood C et al. Pharmacokinetics and lung delivery of PDDS-aerosolized amikacin (NKTR-061) in intubated and mechanically ventilated patients with nosocomial pneumonia. Crit Care. 2009;13(6):R200.
Study period:	**Study Start Date:** 17 MAR 2007 **Study Completion Date:** 06 AUG 2007
Early termination:	Not applicable
Number of subjects:	**Planned:** 30 subjects **Randomized** Not applicable **Analyzed:** 30 subjects
Criteria for evaluation	
Efficacy:	Not applicable

Safety:	Secondary endpoint: Safety was assessed throughout the study by monitoring physical examinations, vital signs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), chest x-rays, ventilator parameters, amikacin serum trough concentrations taken before dosing on each day, concomitant medication use, and adverse events (AEs).
Clinical pharmacology:	Primary endpoint: Serum amikacin concentration values obtained on Day 3 were used to calculate the following parameters using non-compartmental analysis: • C_{max}: Maximum serum amikacin concentration observed from time 0 to 12 h • T_{max}: Time that C_{max} occurred • AUC_{0-12h}: Area under the serum amikacin concentration-vs-time curve from time 0 to 12 h The following urine PK parameters were calculated: • Xu_{0-12h}: Amount of amikacin excreted in urine from 0 to 12 h after dosing • Xu_{12-24h}: Amount of amikacin excreted in urine from 12 to 24 h after dosing • Xu_{0-24h}: Amount of amikacin excreted in urine from 0 to 24 h after dosing Tracheal aspirate and epithelial lining fluid (ELF): Individual tracheal aspirate and ELF amikacin concentrations
Statistical methods:	Safety: Categorical data were summarized as the number and percentage of subjects in each category. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 9.0. Pharmacokinetics: Continuous data and the PK parameters and urine amikacin concentration data were summarized using descriptive statistics: n, mean, standard deviation (SD), standard error, percent coefficient of variation (% CV), median, minimum, maximum, and the 25^{th} and 75^{th} percentiles.
Substantial protocol changes:	Amendment 1 from 03 NOV 2006 introduced the following changes: • Changed the secondary study objectives to eliminate the collection of efficacy parameters and procedures related to those objectives. • A urine pregnancy test at screening was eliminated and trough serum amikacin concentrations throughout the treatment period were further defined. • The ventilator parameters were further defined to include: ventilator

mode, pressure support level, FiO_2, peak inspiratory pressure, plateau inspiratory pressure, positive end expiratory pressure, mean air pressure, peak inspiratory flow rate, rate spontaneous/mechanical, Vt spontaneous/mechanical, I:E ratio (mechanical breaths only), and ramp or square waves.

- Acceptable contraceptive requirements were added to the eligibility criteria.

Amendment 2 from 20 FEB 2007 introduced the following changes:

- Redefined several exclusion criteria to enhance subject recruitment and clarified the Day 3 BAL procedure

Amendment 3 from 10 JUL 2007 introduced the following changes:

- Allowed the inclusion of subjects with gram-negative nosocomial pneumonia and acute renal failure (ARF) treated by continuous veno-venous hemodiafiltration (CVVHDF) for one study center in France

Amendments 4 and 5 from 31 AUG 2007 and 16 NOV 2007, respectively, introduced the following changes:

- Expanded enrollment of subjects with gram-negative nosocomial pneumonia and acute renal failure treated by CVVHDF for two additional study centers in the United States

Subject disposition and baseline

Thirty subjects were enrolled in the study. The mean age was 46.8 years and ranged from 19 to 76 years. The majority of subjects were male (76.7%) and Caucasian (73.3%). The mean (SD) height across the subject population was 175.44 (10.91) cm, the mean (SD) weight was 84.47 (13.64) kg, and the mean (SD) body mass index (BMI) was 27.41 (3.66) kg/m^2. The mean daily serum creatinine level ranged from 0.65 mg/dL to 1.19 mg/dL in all subjects tested from Day 0 to Day 10 of the treatment period.

All 30 subjects were included in the safety population and 28 subjects were included in the PK population.

The mean duration of treatment was 6.27 days. Twenty-one subjects were treated for 5-8 days, 2 subjects were treated for 9 days, and 7 subjects were treated for less than 5 days. The mean ± SD, the minimum, and the maximum durations for on-ventilator and handheld dosing were 36.8 ± 13.8 min, 10 min, and 105 min, respectively.

Efficacy evaluation

Not applicable.

Safety evaluation

Of the 30 subjects who comprised the safety population for this study, 13 subjects terminated early from the study as follows. Five subjects died, 1 subject was lost to follow-up, 1 was listed as the physician's decision (there was no organism in BAL on Day 3), and 6 were listed as "other." The reasons for "other" for these 6 subjects were: 4 subjects were transferred or discharged to a rehabilitation facility, 1 was transferred to another hospital, and 1 received a tracheostomy and therefore unable to use the handheld device.

A total of 354 AEs were reported during this clinical study of which 291 AEs were expected and 63 were unexpected. Expected AEs in ventilated subjects with pneumonia were defined as untoward clinical occurrences that were perceived by the investigator to occur with reasonable frequency and severity, were independent of study medication administration, and would have been reasonably expected in the day-to-day care of subjects with pneumonia who are treated in an intensive care unit (ICU) with mechanical ventilation. Examples of AEs that are expected during the hospital course of nosocomial pneumonia (ie, critically ill) subjects included, but were not limited to, agitation, delirium, skin breakdown, hoarseness following extubation, cough, clinically insignificant deviations in laboratory or blood gas parameters, intolerance of gastric feeding, and gastrointestinal bleeding.

There were 63 unexpected AEs reported by a total of 24 subjects. Six subjects had no AEs other than those expected for ventilator-associated pneumonia (VAP), hospital-acquired pneumonia (HAP), and healthcare-associated pneumonia (HCAP). The most commonly reported unexpected AEs were depression reported by 4 out of 30 subjects (13.3%), deep vein thrombosis reported by 3 out of 30 subjects (10.0%), nausea reported by 3 out of 30 subjects (10.0%), and hypertension reported by 3 out of 30 subjects (10.0%).

There were 11 severe AEs reported in 9 subjects: sepsis (2 instances), cardiac arrest (2 instances), and 1 instance of each of the following: bacterial meningitis, dysphagia, ventricular arrhythmia, anoxic encephalopathy, epilepsy, hypoglycemia, and acute renal failure (ARF).

There were no AEs that were reported as being related to the study device. Three AEs in 2 subjects (bronchospasm [1 subject], and ARF and increased blood creatinine [1 subject]) were considered possibly related to the study medication.

There were 8 subjects who experienced 10 serious AEs (SAEs), including 5 deaths, during the course of the study. None of the deaths were associated with the use of the study medication or study device. Three subject deaths were attributed to causes in the system organ class of infections and infestations (in 2 instances, the reported cause of death was sepsis and in 1 instance the reported cause of death was bacterial meningitis). There was 1 death attributed to ventricular arrhythmia and 1 to anoxic encephalopathy. There was 1 SAE of ARF that was considered possibly related to study drug in this study.

During the course of the study, abnormal serum creatinine levels were reported for 19 subjects, of whom 3 had clinically significant elevations. Of these 3 subjects, 1 had a medical history of ongoing ARF; another had a medical history of chronic renal failure, and the third experienced renal failure during the study. Only 1 subject, a 75 year-old female, had an increased serum creatinine level that was an AE considered possibly related to study drug. The increased serum creatinine level in this subject on Day 4 (2.2 mg/dL) preceded ARF on Day 5. Both the events resolved. The subject had an ongoing history of

ARF 13 days before her first dose. The subject's serum creatinine on Day 1 (1.0 mg/dL) was within the normal range (0.4-1.2 mg/dL).

Twenty-five of the 30 subjects had abnormal elevations in white blood cell (WBC) counts at screening. Of these 25 elevations, 24 were considered clinically significant and 19 were due to their pneumonia. The WBC count in 7 subjects declined from the abnormal elevation at the screening to within normal range at early withdrawal or follow-up.

Fifteen subjects had improvement in their respiratory assessment (clinical signs and symptoms) at follow-up as compared to the assessment at screening. There was only 1 subject with a respiratory assessment at follow-up who was reported as having worsened as compared to their assessment at screening. Of the 30 subjects examined, 14 had improvement in their neurological assessment at follow-up as compared to the assessment at screening. Fourteen subjects in total showed an improvement in chest x-rays to a normal finding (n=6) or had no clinically significant chest x-ray findings (n=8) at follow-up or early termination. Nine subjects either did not have a chest x-ray performed (n=6) or no results were reported (n=3), and 7 subjects continued to have clinically significant chest x-ray findings at follow-up or early termination.

Thirteen subjects had a temperature of 39ºC or greater during the treatment period. All but 7 subjects had a heart rate of 105 beats per min or greater, and all but 12 subjects had a respiration rate of 30 breaths per min or greater during the treatment period. One subject had a respiration rate as low as 8 breaths per min during the treatment period.

Of the 30 subjects enrolled in this study, 30 were receiving at least 1 prior antimicrobial medication. The total number of prior medications administered was 102. The most commonly used prior antimicrobial medications were vancomycin and cefepime used by 17 (56.7%) and 13 (43.3%) of the subjects, respectively. All 30 subjects continued receiving daily antimicrobials after the start of the study. The total number of daily antimicrobial medications administered was 111. The most commonly used daily antimicrobial medications were cefepime and vancomycin used by 14 (46.7%) and 13 (43.3%) of the subjects, respectively.

The total number of concomitant medications administered on or after the date of study medication administration was 724. Twenty-four of the 30 (80.0%) subjects used paracetamol and fentanyl. Insulin was used by 21 (70.0%) subjects and furosemide was used by 20 (66.7%) subjects.

Result for ventilator parameters not available.

Clinical pharmacology evaluation

Pharmacokinetic evaluation:

Mean amikacin PK parameters are presented in the Table 1 below.

Table 1: Mean (SE) Amikacin Pharmacokinetic Parameters

Mean (SE) Amikacin Pharmacokinetic Parameters

Serum C_{max} (µg/mL)	0.95 (0.082)
Serum T_{max} (h)	1.71 (0.25)
Serum AUC_{0-12h} (µg•h/mL)	6.94 (0.72)
Urine Xu_{0-12h} (mg)	20.6 (2.91)
Urine Xu_{12-24h} (mg)	21.7 (2.55)
Urine Xu_{0-24h} (mg)	42.3 (4.62)
Tracheal Aspirate Amikacin Concentration (µg/mL)	1,763.9 (259.0)
ELF Amikacin Concentration (µg/mL)	2,408.9 (689.8)

Mean serum amikacin concentrations on Day 3 were maximal between 1 to 3 h after the first dose, with achieved concentrations in the range of 0.8 to 0.9 µg/mL. Mean trough amikacin concentrations were in the range of 0.2-0.3 µg/mL, indicating that PK steady-state had likely been achieved and that little systemic accumulation of amikacin occurred.

Mean serum amikacin C_{max} and T_{max} values indicated that amikacin was relatively rapidly absorbed followed by a decline to consistent, low mean trough serum amikacin concentrations at the end of each dosing, consistent with the expected clearance of amikacin in subjects with normal renal function. The overall systemic exposure to amikacin, as indicated by AUC_{0-12h} and C_{max} values, was low relative to historical data for intravenous (IV) amikacin, as would be expected based on differences in the lung dose achieved with the study medication regimen and systemic dose achieved with IV infusion.

Amounts of amikacin excreted in urine were comparable between dosing intervals, providing evidence of consistent dosing across intervals and additional evidence that PK steady state had been achieved. The mean Xu_{0-24h} value confirmed the relatively low daily systemic amikacin exposure achieved with the study medication regimen, consistent with the serum amikacin PK results described above.

Mean amikacin concentrations in tracheal aspirate and ELF (1764-2408 µg/mL) were orders of magnitude greater than reported following IV administration of amikacin (4.0 µg/mL) to subjects with pneumonia.

ELF amikacin concentrations appeared independent of peak inspiratory flow rate over the range of 30-90 L/min.

Overall conclusions

- In this study, systemic amikacin exposure following inhaled amikacin administration, as indicated by serum amikacin AUC_{0-12h} and C_{max} values, was low relative to IV amikacin administration.
- Urinary excretion of amikacin was comparable between dosing intervals on Day 3 providing evidence of consistent dosing. The total amikacin amount excreted on Day 3 in the urine confirmed relatively low daily systemic amikacin exposure.

- Amikacin concentrations in tracheal aspirate and ELF demonstrated lung amikacin exposure orders of magnitude greater than that reported following IV amikacin administration in subjects with pneumonia.

- Amikacin lung exposure following inhaled amikacin appeared to be independent of inspiratory flow rate.

- There were 8 subjects who experienced 10 SAEs; 5 of these SAEs led to subject's death. Only 1 SAE, ARF, was considered possibly related to the study medication. All other SAEs were considered not related to the study medication or study device.

- There were 24 subjects who reported a total of 63 unexpected AEs and 6 subjects who did not develop any unexpected AEs for mechanically ventilated ICU subjects with pneumonia.

- Three AEs in 2 subjects (bronchospasm [1 subject] and ARF and increased blood creatinine [1 subject]) were considered possibly related to the study medication.

- There were no AEs related to the study device.

- The serum creatinine results during the study were found to be abnormal for 19 subjects but were clinically significant for only 3 subjects, 1 who had a past medical history of ongoing ARF, 1 who had a past medical history of chronic renal failure, and 1 who experienced an AE of renal failure. There was no apparent trend in serum creatinine levels over the course of the study. Three subjects had serum amikacin trough concentrations of 5.6 µg/mL on Days 3; 4.8 and 4.7 µg/mL on Days 6 and 7; and 1.2 µg/mL on Day 2, respectively.