Introduction

The Amikacin Inhale System (BAY41-6551, NKTR-061) is an integrated drug-device combination in clinical development for adjunctive treatment of Gram-negative pneumonia in intubated, mechanically ventilated patients. The Amikacin Inhale System consists of a disposible, proprietary vibrating mesh nebulizer used to aerosolize a specially formulated amikacin inhalation solution (400mg, 3.2 mL of 125 mg/mL, b.i.d. for 10 days). It has been designed for use in two configurations: one for intubated patients (on-vent configuration, Figure 1), and one for patients extubated prior to the end of their 10-day course of therapy (handheld configuration, Figure 2). Results from Phase II studies indicated that high drug concentrations were achieved in both tracheal aspirates and epithelial lining fluid (ELF) with low systemic concentration and no observed renal toxicity [1-3]. The Amikacin Inhale System was modified between the Phase II and III clinical trials to facilitate commercial manufacturing. This study reports the in vitro efficiency of the Amikacin Inhale System, in both on-vent and handheld configurations.

Method

The study parameters for the in vitro on-vent and handheld configurations are presented in Table 1.

In vitro efficiency of the Amikacin Inhale System, a novel integrated drug-device delivery system

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Results and Discussion

The performance characteristics for the Amikacin Inhale System in the on-vent and handheld configurations are shown in Table 2.

For the same dose of amikacin, nebulization time for the handheld configuration (15 ± 5 minutes) was shorter than that in the on-vent configuration (36 ± 16 minutes) due to the difference in operating mode.

Comparable ELDs were observed for on-vent and handheld configurations (Figures 5 and 6).

Mean ELD was 50% ± 9% of nominal dose for on-vent configuration and was comparable with 49% ± 11% for handheld configuration (Table 2).

ELD increased as volume median diameter (VMD) decreased and dosing administration time increased because droplets with larger VMD and higher output rates had greater tendency to be trapped within the system due to impaction.

Data were analyzed using a least-squares method (JMP 8.0, Cary NC) [4].

Lower and upper (+ standard error) 95% confidence limits defined the minimum and maximum ELD, respectively, for a given combination of VMD and dosing time (Figures 7 and 8).

Minimum achievable ELD was 25-58% of nominal dose (Figure 7) for the on-vent configuration and 35-64% of nominal dose for the handheld configuration (Figure 8).

Based on Phase I and II clinical data [1-3, 5], it is likely that the ELDs for the Amikacin Inhale System in either configuration will exceed the MIC of Gram-negative respiratory tract pathogens in ICU patients with pneumonia.

Conclusions

The study results demonstrated that the Amikacin Inhale System can achieve highly efficient delivery of amikacin in both configurations: on-vent with breath synchronization and handheld with continuous nebulization. Comparable ELDs were obtained in both configurations, indicating that no dose adjustment was required when switching from the on-vent to the handheld configuration.

References