Pharmacokinetics of Vancomycin in Plasma and Sputum Following Pulmonary Administration in Cystic Fibrosis Patients with Persistent Methicillin-Resistant *Staphylococcus Aureus* Infection

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INTRODUCTION

In the past decade, methicillin-resistant *Staphylococcus aureus* (MRSA) lung infection has become increasingly common in cystic fibrosis (CF) patients, with a prevalence of almost 30 % in the United States [1]. Persistent MRSA infection in CF patients has been associated with a faster decline of lung function [2,3], increase in hospitalizations [3] as well as shortened life-expectancy [4].

To address this need, a high performance, engineered, inhalation powder formulation of vancomycin hydrochloride, AeroVanc, was developed and studied in a randomized, double-blind, placebo-controlled phase II clinical study in 87 CF patients with persistent MRSA lung infection. Cohort 1 enrolled 40 patients, randomized (1:1) to receive 28 days of either 32 mg (two 16 mg AeroVanc capsules) bid or placebo. Cohort 2 enrolled 47 patients, randomized (1:1) to receive 28 days of either 64 mg (four 16 mg AeroVanc capsules) bid or placebo.

Pharmacokinetics were evaluated in a subgroup of 27 patients (13 active, 14 placebo) using sputum and plasma vancomycin concentrations. Only vancomycin-treated patients are presented.

METHODS

The pre-dose PK samples of plasma and sputum were collected within 60 minutes prior to the start of dosing on Day 1 (First Dose), Day 8 and Day 29. Post-dose plasma and sputum PK samples were collected 0.25, 1, 2, and 4 hours (all ± 10 minutes) post-dose on Day 1, 8 and 29.

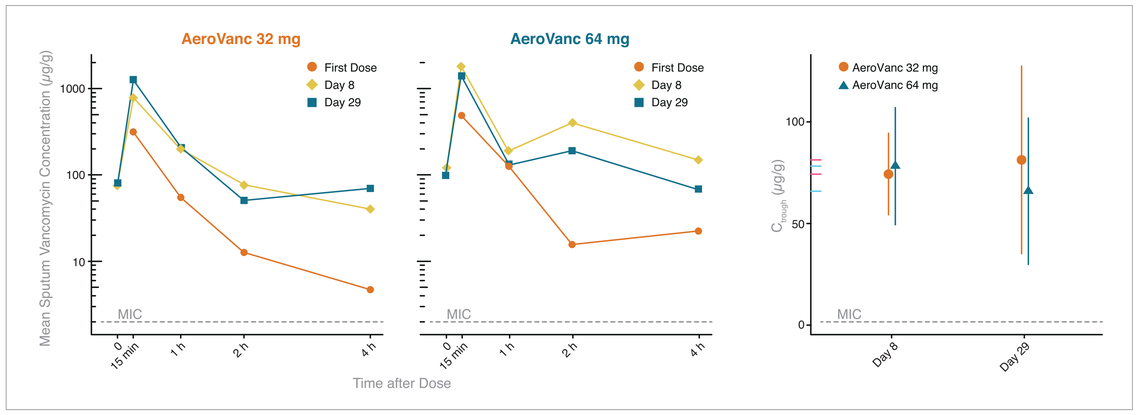
Concentrations of vancomycin in sputum were assayed using a validated LC/MS/MS method. The lower limit of quantification for this method was 0.5 µg/g [ALM-096-03/C].

Concentrations of vancomycin in plasma were assayed using a validated LC/MS/MS method. The lower limit of quantification for this method was 10.0 ng/mL [ALM-095-01].

Pharmacokinetic parameters were derived using noncompartmental methods employing WinNonlin® Phoenix version 6.3 (Pharsight Corp, St. Louis, MO).

RESULTS

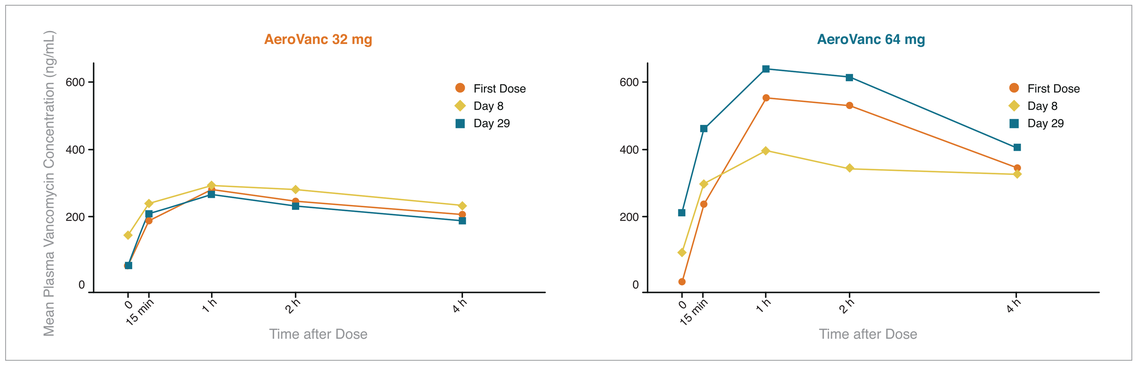
FIGURE/TABLE 1: MEAN SPUTUM VANCOMYCIN CONCENTRATIONS FOLLOWING INHALATION DELIVERY OF 32 MG BID OR 64 MG BID AEROVANC THROUGH 4 HOURS POST-DOSE (FIGURE LEFT, CENTER). MEAN TROUGH CONCENTRATION OF VANCOMYCIN IN SPUTUM AT DAY 8 AND 29 (FIGURE RIGHT). MEAN (CV %) SPUTUM PK PARAMETERS FOR AEROVANC (TABLE).



Sputum PK Parameter	Day 1 32 mg BID	Day 1 64 mg BID	Day 8 32 mg BID	Day 8 64 mg BID	Day 29 32 mg BID	Day 29 64 mg BID
Number of Subjects	6	5	6	3	2	2
C_{max} (µg/g)	316 (67.5)	531 (48.4)	767 (60.7)	1790 (84.1)	1270 (NC[b])	1400 (NC[b])
C_{max}/Dose (µg/g/mg)	9.89 (67.5)	8.29 (48.4)	24.0 (60.7)	27.9 (84.1)	39.5 (NC[b])	21.8 (NC[b])
T_{max}[a] (h)	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.25 (0.25-0.25)
C_{trough} (µg/g)	-	-	74.5 (165)	119 (80.8)	81.4 (114)[g]	99.0 (NC[b])
C_{trough} /MIC ([µg/g)/(µg/mL])[f]	-	-	37.3 (165)	59.3 (80.8)	40.7 (114)[g]	49.5 (NC[b])
AUC_{0-4} (h· µg/g)	194 (46.9)	284 (26.1)	647 (67.6)	1430 (91.3)	822 (NC[b])	988 (NC[b])
AUC_{0-4}/Dose (h· µg/g/mg)	6.05 (46.9)	4.44 (26.1)	20.2 (67.6)	22.4 (91.3)	25.7 (NC[b])	15.4 (NC[b])
AUC_{0-12} (h· µg/g)[e]	-	-	1100 (80.3)	2460 (91.9)	1480 (NC[b])	1660 (NC[b])
AUC_{0-12}/MIC ([h· µg/g)/(µg/mL])[f]	-	-	549 (80.3)	1230 (91.9)	741 (NC[b])	829 (NC[b])
$Cavg_{0-4}$[c] (µg/g)	48.4 (46.9)	71.0 (26.1)	162 (67.6)	358 (91.3)	206 (NC[b])	247 (NC[b])
C_{max}–Acc[d]	-	-	3.60 (94.6)	2.09 (NC[b])	5.96 (NC[b])	3.14 (NC[b])
AUC_Acc[d]	-	-	3.86 (82.2)	2.21 (NC[b])	6.47 (NC[b])	3.12 (NC[b])

[a] T_{max} was represented as Median (Range)
[b] Number of subjects =2, NC = Statistics not calculated when N<3
[c] $Cavg_{0-4}$ is the average concentration of the 4-hour sampling period, calculated by AUC_{0-4}/4
[d] C_{max}–Acc and AUC_Acc are accumulation ratios, calculated using PK parameters (C_{max} and AUC_{0-4}) of Day 8 or Day 29 divided by that of Day 1 from the same subject
[e] 12-hour concentration was imputed to the pre-dose value for the calculation of AUC_{0-12} of multiple-dose administration (Visits 8 and 29). (AUC_{0-12} value using imputed 12-hour concentration value is a reasonable estimate if steady-state can be presumed, otherwise AUC_{0-12} is underestimated, and therefore AUC/MIC is a conservative estimate)
[f] MIC = Minimum inhibitory concentration (MIC) of vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA) (2 µg/mL) [5]
[g] Number of Subjects = 3

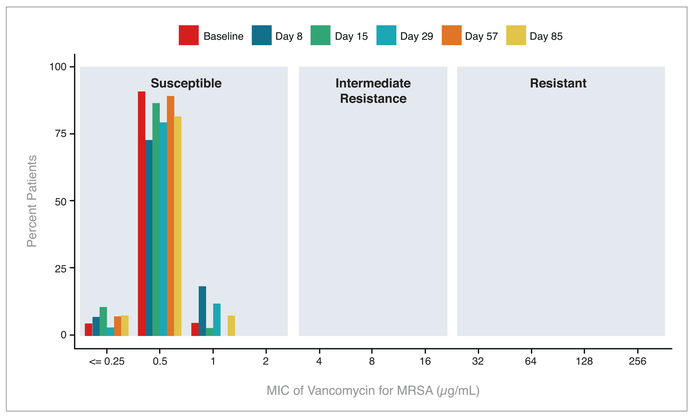
FIGURE/TABLE 2: MEAN PLASMA VANCOMYCIN CONCENTRATIONS FOLLOWING INHALATION DELIVERY OF 32 MG BID OR 64 MG BID AEROVANC THROUGH 4 HOURS POST-DOSE (FIGURES). MEAN (CV %) PLASMA PK PARAMETERS FOR AEROVANC (TABLE).



Plasma PK Parameter	Day 1 32 mg BID	Day 1 64 mg BID	Day 8 32 mg BID	Day 8 64 mg BID	Day 29 32 mg BID	Day 29 64 mg BID
Number of Subjects	6	6	6	3	2	2
C_{max} (µg/mL)	0.283 (68.7)	0.589 (37.8)	0.315 (70.5)	0.435 (19.5)	0.266 (NC[b])	0.694 (NC[b])
C_{max}/Dose (µg/mL/mg)	0.00884 (68.7)	0.00920 (37.8)	0.00985 (70.5)	0.00679 (19.5)	0.00833 (NC[b])	0.0108 (NC[b])
T_{max}[a] (h)	1.00 (1.00-2.00)	1.00 (1.00-2.00)	1.00 (0.25-2.00)	1.00 (1.00-4.00)	1.00 (1.00-1.00)	1.5 (1.00-2.00)
C_{trough}	-	-	0.146 (133)	0.0568 (46.1)	0.0920 (11.4)	0.213(NC[b])
AUC_{0-4} (h· µg/mL)	0.914 (78.7)	1.73 (33.4)	1.04 (80.2)	1.34 (21.4)	0.880 (NC[b])	2.13 (NC[b])
AUC_{0-4}/Dose (h· µg/mL/mg)	0.0286 (78.7)	0.0271 (33.4)	0.0326 (80.2)	0.0210 (21.4)	0.0275 (NC[b])	0.0333 (NC[b])
C_{max}–Acc[c]	-	-	1.13 (16.7)	0.636 (NC[b])[d]	1.22 (NC[b])	0.937 (NC[b])
AUC_Acc[c]	-	-	1.15 (22.8)	0.695 (NC[b])[d]	1.38 (NC[b])	0.991 (NC[b])

[a] T_{max} was represented as Median (Range)
[b] NC = Statistics not calculated when N<3
[c] C_{max}–Acc and AUC_Acc are accumulation ratios, calculated using PK parameters (C_{max} and AUC_{0-4}) of Day 8 or Day 29 divided by that of Day 1 from the same subject
[d] Number of Subjects = 2

FIGURE 3: MINIMUM INHIBITORY CONCENTRATION (MIC) OF VANCOMYCIN IN SPUTUM DURING TREATMENT AND OBSERVATION PERIOD



CONCLUSION

- High sputum to plasma exposure ratios indicated significant and dose proportional lung exposure with minimal exposure in systemic circulation after multiple dose AeroVanc administration
- There was no apparent plasma vancomycin accumulation over time, but significant sputum vancomycin accumulation was observed, contributing to the high therapeutic concentrations achieved
- Lung concentrations of vancomycin were consistently above MIC of vancomycin for MRSA (2 µg/ml), with an estimated AUC_{0-12}/MIC > 500 and an estimated C_{trough}/MIC > 30
- No shift in the MIC distribution was observed during treatment (28 days) and through follow-up (85 days)
- Further PK analysis of inhaled vancomycin in a larger population and over multiple cycles should be performed in future clinical studies (planned for 2017)

ACKNOWLEDGMENT

Research reported was supported by the Cystic Fibrosis Foundation Therapeutics Inc., the nonprofit affiliate of the Cystic Fibrosis Foundation, as well as the National Heart, Lung, and Blood Institute of the National Institutes of Health (award number R44HL112393). The content is solely the responsibility of Savara and may not represent the official views of either organization.

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