

Serum pharmacokinetic parameters (C_{max} , AUC_{0-8} , and $AUC_{0-\infty}$) were analyzed for differences between delivery systems using a repeated measures analysis of variance. The statistical model included study period and delivery systems as fixed effects and subject as the random effect. The carryover effect from
5 treatment period 1 to 2 was also investigated. The significance level was set at $\alpha = 0.05$, and tests of significance were two-sided.

Additional deposition measures of interest, nebulization time, serum tobramycin concentrations and pharmacokinetic parameters were summarized and evaluated descriptively for apparent differences between aerosol delivery systems.

10 Study Drug Administration

All subjects were successfully dosed according to the randomization schedule for the study, and all subjects received and completed both inhalation administrations. All subjects received single doses of TOBI 300 mg and TOBI 60 mg during the study.

15 Deposition of Radiolabeled Tobramycin

Tobramycin deposition results indicated that the Aerodose system was more efficient than the PARI LC PLUS system. The Aerodose system with TOBI 60 mg delivered a greater percentage of the dose to the lungs (mean \pm SD = 34.8 ± 10.1 %) than the PARI system with TOBI 300 mg (8.2 ± 3.6 %), and the difference was
20 statistically significant ($p = 0.005$) (see Table 12 below). Results from the analysis ($n = 9$) that excluded data from one patient were similar (means = 35.4% vs. 9.1% for Aerodose and PARI systems, respectively; $p = 0.008$).

The actual amount of drug delivered to the lungs (Table 13 below) was slightly but not significantly less ($p = 0.202$) using the Aerodose inhaler (20.9 ± 6.0
25 mg) than using the PARI inhaler (24.5 ± 10.7 mg). Excluding subject 1007, the analysis showed significantly less ($p = 0.04$) deposition of the Aerodose 60 mg dose (21.2 mg) than the PARI 300 mg dose (27.2 mg).

TABLE 12. MEAN (SD) PERCENTAGE DEPOSITION OF THE METERED TOBI DOSE

Zone of Deposition	Intent to Treat (n = 10)		Excluding Subject 1007 (n = 9)		p-value*
	TOBI 300mg PARI LC PLUS	TOBI 60mg AeroDose	TOBI 300mg PARI LC PLUS	TOBI 60mg AeroDose	
Whole lung	8.2 (3.6)*	34.8 (10.1)*	9.1 (2.2)	35.4 (10.5)	0.005
central	2.4 (1.2)	10.1 (4.0)	2.7 (0.9)	10.2 (4.2)	
intermediate	2.7 (1.2)	11.6 (3.6)	3.0 (0.8)	11.8 (3.7)	
peripheral	3.1 (1.3)	13.2 (3.4)	3.5 (0.7)	13.4 (3.5)	
ratio: peripheral / central	1.2 (0.5)	1.4 (0.4)	1.4 (0.3)	1.4 (0.4)	
Oropharynx (including esophagus and stomach)	14.4 (6.7)	31.5 (11.6)	16.0 (4.7)	31.5 (12.3)	
Inhaler	42.6 (6.7)	15.2 (8.4)	43.5 (6.4)	15.1 (8.9)	
Exhalation filter	31.6 (10.9)	16.9 (5.6)	28.3 (2.7)	16.3 (5.6)	
PARI-specific:					
mouthpiece	1.0 (0.5)		1.0 (0.5)		
T-piece	2.0 (0.6)		2.0 (0.5)		
tissue	0.0 (0.1)		0.0 (0.1)		
scavenger filter	0.1 (0.1)		0.1 (0.1)		
AeroDose-specific:					
box		1.7 (1.5)		1.6 (1.6)	
tissue		0.0 (0.1)		0.0 (0.1)	

* Wilcoxon matched-pairs signed ranks test on intent to treat dataset. Excluding Subject 1007: p = 0.008. Statistical significance: p ≤ 0.05.

The Aerodose inhaler deposited proportionally more (Table 12 above) tobramycin in the lungs than in the oropharynx (mean 34.8 % vs. 31.5 % of the 60 mg dose), while the PARI LC PLUS nebulizer deposited less tobramycin in the lungs than in the oropharynx (mean 8.2 % vs. 14.4 % of the 300 mg dose). The ratio of lung to oropharyngeal deposition (whole lung deposition divided by oropharynx deposition in Table 12 above) was approximately 1.1 for the Aerodose inhaler compared to approximately 0.6 for the PARI LC PLUS nebulizer.

Regional deposition within the lung was predominantly peripheral and very similar for both inhalers (ratio of radioactivity in peripheral to central zones: Aerodose = 1.4 ± 0.4 ; PARI LC PLUS = 1.2 ± 0.5).

Substantially less tobramycin was deposited on the Aerodose inhaler (15.2 ± 8.4 %; 9.1 ± 5.1 mg; Tables 4 and 5, respectively) and exhalation filter (16.9 ± 5.6 %; 10.1 ± 3.3 mg) than on the PARI LC PLUS nebulizer (42.6 ± 6.7 %; 127.8 ± 20.0 mg) and filter (31.6 ± 10.9 %; 94.8 ± 32.7 mg). No more than 2% of the metered dose was deposited on inhaler-specific surfaces or tissue paper used by subjects.

TABLE 13. MEAN (SD) AMOUNT (MG) OF DEPOSITION OF THE
METERED TOBI DOSE

Zone of Deposition	Intent to Treat (n = 10)		Excluding Subject 1007 (n = 9)		p-value*
	TOBI 300mg PARI LC PLUS	TOBI 60mg AeroDose	TOBI 300mg PARI LC PLUS	TOBI 60mg AeroDose	
Whole lung	24.5 (10.7)*	20.9 (6.0)*	27.2 (6.7)	21.2 (6.3)	0.202
central	7.3 (3.6)	6.0 (2.4)	8.0 (2.8)	6.1 (2.5)	
intermediate	8.0 (3.7)	6.9 (2.1)	8.9 (2.5)	7.1 (2.2)	
peripheral	9.3 (3.8)	7.9 (2.1)	10.4 (2.0)	8.1 (2.1)	
Oropharynx (including esophagus and stomach)	43.3 (20.2)	18.9 (6.9)	48.1 (14.0)	18.9 (7.4)	
Inhaler	127.8 (20.0)	9.1 (5.1)	130.5 (19.2)	9.0 (5.4)	
Exhalation filter	94.8 (32.7)	10.1 (3.3)	84.8 (8.1)	9.8 (3.4)	
PARI-specific:					
mouthpiece	3.0 (1.4)		3.1 (1.5)		
T-piece	6.1 (1.7)		5.9 (1.6)		
tissue	0.1 (0.2)		0.1 (0.2)		
scavenger filter	0.4 (0.4)		0.4 (0.4)		
AeroDose-specific:					
box		1.0 (0.9)		1.0 (0.9)	
tissue		0.0 (0.1)		0.0 (0.1)	

* Wilcoxon matched-pairs signed ranks test on intent to treat dataset. Excluding Subject 1007: p = 0.04. Statistical significance: p ≤ 0.05.

Nebulization Time

The nebulization time (i.e., time required from first tidal breath until the nebulizer ran dry) was significantly shorter (p = 0.005) for the Aerodose delivery system (mean ± SD = 5.70 ± 1.16 minutes) than for the PARI LC PLUS system (20.40 ± 3.47 minutes) (Table 14 below).

TABLE 14. MEAN (SD) NEBULIZATION TIME

Nebulization Time* Parameter	Intent to Treat (n = 10)		p-value
	TOBI 300mg PARI LC PLUS	TOBI 60mg AeroDose	
Nebulization Time (minutes):			
Mean	20.40	5.70	0.005
SD	3.47	1.16	
Minimum	17.0	4.0	
Maximum	29.0	8.0	
no. subjects	10	10	

Serum Tobramycin Concentrations and Pharmacokinetic Parameters

Administration of TOBI 300 mg using the PARI LC PLUS delivery system produced higher mean serum tobramycin concentrations, a higher mean C_{max} , and a greater $AUC_{(0-8)}$ than administration of TOBI 60 mg using the Aerodose delivery system. The mean time to maximum tobramycin concentration (T_{max}) was similar for the two delivery systems.

Serum tobramycin concentrations for all subjects were below quantifiable limits before dosing in both period 1 and period 2. Figures 1 through 20 graphically illustrate serum tobramycin concentrations before and after period 1 and period 2 dosing for all individual subjects.

After dosing, two subjects had serum tobramycin concentrations that could not be measured (i.e., results were below the quantifiable limit of 0.20 $\mu\text{g/mL}$) during one of the two treatment periods. These two subjects were inevaluable for pharmacokinetic analysis during the period indicated but provided evaluable results for the alternate period.

Consistent with the high efficiency of the Aerodose system, mean serum tobramycin concentrations were slightly lower throughout the 8-hour postdose observation period after delivery of TOBI 60 mg using the Aerodose system than after delivery of TOBI 300 mg using the PARI LC PLUS system (Table 15 below).

Maximum plasma concentrations for both regimens were reached within 2 hours after the end of inhalation (TOBI 300 mg and PARI inhaler: 1 hr and 2 hr means = 0.63 $\mu\text{g}/\text{mL}$; TOBI 60 mg and Aerodose inhaler: 2 hr mean = 0.48 $\mu\text{g}/\text{mL}$). By 8 hours after the end of inhalation, the plasma concentrations were below the limit of
5 quantitation in 5 subjects after the Aerodose inhaler and in two subjects after the PARI LC PLUS nebulizer.

TABLE 15. SERUM TOBRAMYCIN CONCENTRATIONS AND PHARMACOKINETIC PARAMETERS

Parameter*	Intent to Treat (n = 10)	
	TOBI 300mg PARI LC PLUS ^a	TOBI 60mg AeroDose ^b
Serum Tobramycin (µg/mL): Time Before and After Dosing:		
Predose	0.00 (0.00) 9	0.00 (0.00) 9
30 minutes	0.42 (0.24) 9	0.22 (0.23) 9
1 hour	0.63 (0.29) 9	0.41 (0.22) 9
2 hours	0.63 (0.25) 9	0.48 (0.20) 9
4 hours	0.50 (0.16) 9	0.38 (0.10) 9
8 hours	0.22 (0.14) 9	0.13 (0.12) 9
Pharmacokinetic Parameters:		
C _{max} (µg/mL)	0.677 (0.279) 9	0.482 (0.201) 9
T _{max} (hr)	2.213 (0.923) 9	2.207 (0.788) 9
T _{1/2} (hr)	4.269 (1.058) 9	6.071 (3.357) 9
AUC ₍₀₋₈₎ (µg/mL•hr)	3.622 (1.319) 9	2.553 (0.989) 9
AUC _(0-∞) (µg/mL•hr)	5.273 (1.699) 9	4.630 (0.967) 9
Pharmacokinetic Parameters Normalized to Dose:		
C _{max} (µg/mL)/mg	0.002 (0.001) 9	0.008 (0.003) 9
AUC ₍₀₋₈₎ (µg/mL•hr)/mg	0.012 (0.004) 9	0.043 (0.016) 9
AUC _(0-∞) (µg/mL•hr)/mg	0.018 (0.006) 9	0.077 (0.016) 9
* Cell entries are mean, (SD), no. of subjects.		
a TOBI 300 mg summary statistics exclude BQL results for Subject 1007 throughout period 2.		
b TOBI 60 mg summary statistics exclude BQL results for Subject 1006 throughout period 1.		

Pharmacokinetic Results

The mean of the maximum tobramycin concentrations for all subjects (C_{max} in Table 15 above) was greater after TOBI 300 mg delivered by the PARI LC PLUS system (mean ± SD = 0.677 ± 0.279 µg/mL) than after TOBI 60 mg delivered by the Aerodose system (0.482 ± 0.201 µg/mL). This mean difference in log C_{max} was statistically significant (p = 0.0018), and there was no evidence to suggest the presence of a carryover effect in C_{max} (p = 0.6400). The Aerodose inhaler was more

efficient than the PARI LC PLUS nebulizer based on C_{max} results adjusted for TOBI dose administered (TOBI 300 mg with PARI LC PLUS = 0.002 ± 0.001 ($\mu\text{g/mL}$)/mg; TOBI 60 mg with Aerodose = 0.008 ± 0.003 ($\mu\text{g/mL}$)/mg).

The time to maximum tobramycin concentrations (T_{max}) was virtually
5 identical for the two delivery systems (mean = 2.213 hours for PARI LC PLUS and 2.207 hours for Aerodose systems in Table 15 above). T_{max} results in the present study were consistent with observations in a previous study¹⁵ that peak serum tobramycin concentrations occurred at 1 to 2 hours after inhalation.

The mean elimination half-life ($T_{1/2}$) was 4.269 hours for the PARI LC PLUS
10 system and 6.071 hours for the Aerodose system (Table 7).

The mean area under the serum concentration-time curve through 8 hours
postdose ($AUC_{(0-8)}$) was significantly greater ($p = 0.0002$ on log $AUC_{(0-8)}$) after TOBI 300 mg delivered by the PARI LC PLUS system (3.622 ± 1.319 $\mu\text{g/mL}\cdot\text{hr}$) than after TOBI 60 mg delivered by the Aerodose system (2.553 ± 0.989 $\mu\text{g/mL}\cdot\text{hr}$). There
15 was no evidence ($p = 0.7858$) to suggest the presence of carryover effect in $AUC_{(0-8)}$. The greater efficiency of the Aerodose inhaler was also seen in dose-normalized $AUC_{(0-8)}$ results (TOBI 300 mg with PARI LC PLUS = 0.012 ± 0.004 [$\mu\text{g/mL}\cdot\text{hr}$]/mg; TOBI 60 mg with Aerodose = 0.043 ± 0.16 [$\mu\text{g/mL}\cdot\text{hr}$]/mg).

The mean area under the serum concentration by time curve extrapolated to
20 infinity ($AUC_{(0-\infty)}$ in Table 7 above) was not significantly different ($p = 0.5477$ on log $AUC_{(0-\infty)}$) after administration of TOBI 300 mg using the PARI system (5.273 ± 1.699 $\mu\text{g/mL}\cdot\text{hr}$) than after administration of TOBI 60 mg using the Aerodose system (4.630 ± 0.967 $\mu\text{g/mL}\cdot\text{hr}$). No carryover effect was detected ($p = 0.6006$). The greater efficiency of the Aerodose inhaler was similarly seen in dose-normalized
25 $AUC_{(0-\infty)}$ results (TOBI 300 mg with PARI LC PLUS = 0.018 ± 0.006 [$\mu\text{g/mL}\cdot\text{hr}$]/mg; TOBI 60 mg with Aerodose = 0.077 ± 0.16 [$\mu\text{g/mL}\cdot\text{hr}$]/mg).

Unplanned, exploratory analyses suggested that female subjects achieved slightly higher C_{max} , $AUC_{(0-8)}$ and $AUC_{(0-\infty)}$ results than male subjects after both TOBI 300 mg and TOBI 60 mg treatments.

Extent of Exposure

The duration of exposure to study drug and the dose of study drug were not varied in this study. All 10 subjects received a single 300 mg (5 mL) TOBI dose using the PARI LC PLUS jet nebulizer with the DeVilbiss PulmoAide compressor delivery system (control treatment) on one occasion and a single 60 mg (1 mL) TOBI dose using the Aerodose inhaler (experimental treatment) on a second occasion. Each dose was radiolabeled with up to 10MBq ^{99m}Tc-DTPA and administered in a randomized two-way crossover fashion separated by a 44-hour minimum washout period.

The mean whole lung deposition using the PARI LC PLUS nebulizer was 8.2% (24.5 mg) of the 300 mg TOBI dose. The mean whole lung deposition using the Aerodose inhaler was 34.8% (20.9 mg) of the 60 mg TOBI dose. A mean of 14.4 % (43.3 mg) and 31.5% (18.9 mg) of the corresponding doses were deposited in the oropharynx using the PARI LC PLUS and Aerodose inhalers, respectively. Both inhaler systems were configured such that each subject's exhaled material was collected and did not escape with radioactive aerosol into the surrounding atmosphere. The PARI LC PLUS nebulizer also included a system to collect any radiolabeled droplets escaping from the nebulizer.

Bronchospasm

In this study, decreases in the relative FEV₁ % predicted $\geq 10\%$ (not clinically significant if $< 20\%$) and $\geq 20\%$ (clinically significant) from predose measurements to 30-minutes postdose measurements with each delivery system were used as indicators of bronchospasm (airway reactivity). Reductions in FEV₁ % predicted $\geq 20\%$ were considered clinically significant for the purposes of the study. No subject had a drop in FEV₁ % predicted $\geq 10\%$ from predose to postdose regardless of delivery system during this study.

Discussion and Overall Conclusions

The study of this example demonstrates that the AeroDoseTM inhaler was more efficient in delivery of aerosolized tobramycin to the lungs of healthy adult volunteers than the approved PARI LC PLUS jet nebulizer with DeVilbiss

PulmoAide compressor. Since the Aerodose inhaler is breath-actuated and generates aerosol only during inhalation, proportionally more of the Aerodose dose should be delivered to the lungs than is delivered by the PARI LC PLUS, and there should be minimal wastage of drug by aerosolization during exhalation or by incomplete
5 aerosolization of the contents of the drug reservoir.

During the study, the Aerodose inhaler delivered a significantly greater percentage of the dose to the lungs than the PARI LC PLUS nebulizer (mean 34.8% vs. 8.2%: $p = 0.005$). The actual amount of the dose deposited in the lungs was slightly but not significantly less using the Aerodose inhaler than using the PARI LC
10 PLUS nebulizer (20.9 mg vs. 24.5 mg: $p = 0.202$). These data demonstrate that the Aerodose inhaler delivered nearly as much tobramycin to the lungs as the PARI LC PLUS nebulizer despite nebulizing one-fifth the amount of tobramycin.

Approximately 32% of the Aerodose dose was wasted on the inhaler and exhalation filter combined. By contrast, more than 74% of the PARI LC PLUS dose
15 was wasted by deposition on the inhaler and exhalation filter.

When the Aerodose inhaler was used, 15.2% (9.1 mg) of the 60 mg TOBI dose remained deposited on the inhaler, and 16.9% (10.1 mg) was deposited on the exhalation filter. Since no aerosolization occurred during exhalation when the Aerodose was used, the observed deposition could have been due only to seepage
20 through the mouth-inhaler seal or to residual radiolabeled tobramycin inhaled but immediately exhaled and not deposited in either the lungs or the oropharynx (including esophagus and stomach). Four subjects were noted to have either experienced problems maintaining a seal around the mouthpiece of the Aerodose inhaler or reported that the inhaler failed to nebulize one of the two aliquots of the
25 dose solution. These subjects had approximately 47%, 19%, 53%, and 26%, respectively, of the 60 mg dose deposited on the inhaler and exhalation filter combined. The highest two of these figures were above the range noted for the rest of the subjects (ranging from 17% to 40% deposited on inhaler and exhalation filter combined). Problems with incomplete nebulization or wide variation in subject

inhalation effectiveness may have contributed to the amount of wastage of drug during Aerodose usage in the present study.

By comparison, when the PARI LC PLUS jet nebulizer was used, 42.6% (127.8 mg) of the 300 mg TOBI dose remained deposited on the inhaler, and 31.6%
5 (94.8 mg) was deposited on the exhalation filter. Presumably, most or all of the exhalation filter deposition was due to continued aerosolization and consequent loss of drug while subjects exhaled.

Thus, both the Aerodose inhalers and PARI LC PLUS nebulizers wasted drug product in the present study by reason of retention of radiolabeled drug on or in the
10 inhaler or deposition of drug on the exhalation filter (an average of approximately 19 of 60 mg wasted when the Aerodose inhaler was used and approximately 223 of 300 mg wasted when the PARI LC PLUS nebulizer was used). The proportion of the total dose wasted using the Aerodose inhaler was less than half of that wasted using the approved PARI LC PLUS nebulizer.

15 The Aerodose inhaler also appeared to exhibit better "targeting" or delivery of the dose to the lungs, the target site of the usual *P. aeruginosa* infection in cystic fibrosis patients, than the PARI LC PLUS nebulizer. The Aerodose inhaler deposited slightly more tobramycin in the lungs than in the oropharynx, esophagus, and stomach (lungs 34.8% vs. 31.5% of the 60 mg dose). By comparison, the PARI LC
20 PLUS nebulizer deposited proportionally less of the dose in the lungs than in oropharynx, esophagus, and stomach (lungs 8.2% vs. 14.4% of the 300 mg dose). The ratio of lung to oropharyngeal, esophagus, and stomach combined was approximately 1.1 for the Aerodose inhaler and 0.6 for the PARI LC PLUS nebulizer.

25 In addition to greater efficiency by greater delivery of drug to the lungs and proportionally greater targeting of the lungs, the Aerodose inhaler was also anticipated to be more efficient by reason of proportionally greater delivery of tobramycin to peripheral rather than central lung regions. The Aerodose particle MMD is smaller (mean MMD = 4.0 μm) than that produced by the PARI LC PLUS
30 nebulizer (mean MMD = 4.8 μm), so the expectation was that the Aerodose inhaler

would deposit a greater proportion of aerosol generated during inhalation in the peripheral airways than the PARI LC PLUS. During the study, the Aerodose inhaler deposited 13.2% (7.9 mg) of the 60 mg dose in the peripheral airways, while the PARI LC PLUS nebulizer deposited 3.1% (9.3 mg) in peripheral airways. Although
5 the Aerodose inhaler achieved proportionally greater peripheral deposition than the PARI LC PLUS nebulizer, both inhalers fell short of amounts predicted for peripheral deposition based on theoretical considerations (Aerodose estimated to peripherally deposit 60% (36 mg) of the 60 mg dose = 1.0 mL fill volume • 0.95 aerosolization • 0.62 respirable particles; PARI LC PLUS estimated to peripherally
10 deposit 16% (48 mg) of the 300 mg dose = 5.0 mL fill volume • 0.64 aerosolization • 0.44 respirable particles).

Results of the study also showed that the Aerodose inhaler required significantly less nebulization time than the PARI LC PLUS nebulizer (mean 20.4 vs. 5.7 minutes, respectively). The 5.7 minute average nebulization time for the
15 Aerodose inhaler did not include the amount of time needed to fill the drug reservoir before nebulization of the second aliquot. Based on nebulization time results and other inhaler features including portability, ease of use, and lack of a need for a compressor, it is anticipated that the Aerodose inhaler would improve patient compliance.

20 Serum tobramycin concentrations, maximum concentrations, and extent of absorption were greater after administration of TOBI 300 mg using the PARI LC PLUS nebulizer than after administration of TOBI 60 mg using the Aerodose inhaler. These results appeared to be consistent with amounts of tobramycin deposited in lungs and oropharynx (including esophagus and stomach) combined where systemic
25 absorption occurred (mean tobramycin deposited in lungs and oropharynx combined = 67.8 mg after TOBI 300 mg; mean = 39.8 mg after TOBI 60 mg). Mean serum tobramycin concentrations were higher throughout the 8-hour observation period after administration of TOBI 300 mg using the PARI LC PLUS nebulizer than after administration of TOBI 60 mg using the Aerodose inhaler. Mean C_{max} values were
30 0.677 and 0.482 $\mu\text{g/mL}$ for TOBI 300 mg and TOBI 60 mg, respectively (statistically

significant: $p = 0.0018$). Mean T_{max} results for both inhalers were virtually identical (2.213 and 2.207 hours, respectively). Apparent absorption of tobramycin was significantly greater during the 8-hour postdose period after TOBI 300 mg than after TOBI 60 mg (mean $AUC_{0-8} = 3.622$ and $2.553 \mu\text{g/mL}\cdot\text{hr}$, respectively; statistically significant: $p = 0.0002$), but no treatment differences were noted in $AUC_{0-\infty}$ (TOBI 300 mg and TOBI 60 mg means = 5.273 and $4.630 \mu\text{g/mL}\cdot\text{hr}$, respectively; $p = 0.5499$).

Current results suggested that the 60 mg TOBI dose aerosolized using the Aerodose inhaler produced tobramycin deposition and serum tobramycin concentration results that were significantly or substantially less than results obtained after aerosolization of the approved TOBI 300 mg dose using the PARI LC PLUS nebulizer. Normalized for administered dose, the Aerodose inhaler was substantially more efficient on a per milligram basis in delivery of tobramycin to the systemic circulation than the PARI LC PLUS nebulizer. These results are consistent with the higher deposition (on a milligram basis) in the lung.

Results of the study also showed that single doses of TOBI 300 mg delivered using the PARI LC PLUS jet nebulizer and of TOBI 60 mg delivered using the Aerodose breath actuated nebulizer were safe and well-tolerated by healthy adult male and female volunteers. No instances of bronchospasm were observed, and no notable quantitative changes in pulmonary function were seen. No notable adverse events (AEs) were reported by subjects, and there were no apparent differences between treatment groups in incidence of any AE. Six treatment emergent AEs were reported by 4 subjects, but all events were mild in intensity. Two instances of headache were considered possibly or definitely related to treatment. No clinically significant laboratory results or changes in results were observed. No adverse vital signs, body weights, physical findings, or electrocardiogram results were observed. No evidence of systemic toxicity, as measured by unusually high serum tobramycin concentrations, was observed.