Table 1 Percent of Subjects Reaching Evernimicin Preclinical Targets

	S. pneumonia			*S. aureus*			Enterococci		
Dose (mg/kg)	Stasis	Log drop	90% E_{max}	Stasis	Log drop	90% E_{max}	Stasis	Log drop	90% E_{max}
6	100	100	96	92	72	34	100	100	58
9	100	100	98	97	85	50	100	100	79

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a 50% increase in dose resulted in little change in the number of subjects reaching the preclinical targets.

A second application of this methodology was reported the next year with GW 420867X, a non-nucleoside reverse transcriptase inhibitor of human immunodeficiency virus type 1 (HIV-1) (16). In this study, the authors used two preclinical pieces of information: in vitro protein binding of the drug in human plasma and the distribution of concentrations that inhibit 90% of viral growth (EC_{90}) to test HIV isolates. The pharmacokinetics of GW420867X was then characterized using nonparametric population-based methods with data obtained from a multiple-dose study in normal healthy volunteers. Assuming the pharmacokinetics in healthy volunteers will be reflective of the pharmacokinetics in patients with HIV and that time above the EC_{90} will be the important pharmacodynamic target, the clinical information was then combined with the preclinical information to create a joint model predicting unbound drug concentrations in patients at steady state. Using Monte Carlo simulation, the authors tested three dosing regimens (50, 100, and 200 mg once daily) to determine the percent of subjects with simulated unbound trough drug concentrations greater than 10-times the EC_{90} and EC_{50}. Based on the simulation, each of the doses provided $>95\%$ target attainment when the EC_{50} was less than 10 nM. At the time of publication, the authors indicated that, among the 16 isolates available, all had EC_{50}s less than 8 nM. In summary, by combining relevant preclinical targets with clinical information, Drusano et al. were able to either predict a relevant dosing regimen or to make conclusions about differences in already selected dosing regimens.

5. CONCLUSIONS

Preclinical pharmacokinetic–pharmacodynamic modeling has most value early in drug development, prior to Phase 2, when the clinically useful dosing regimen is still undefined. At this early stage, the pharmacokinetics in humans can be estimated using allometric scaling (Chapter 2). Then, given