Pharmacokinetics and Pharmacodynamics of BV100 in Neutropenic Mouse Lung Infection Models

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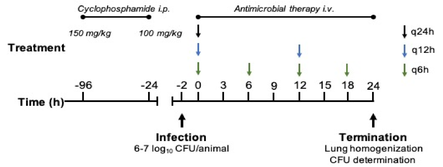
INTRODUCTION

BV100 (rifabutin for infusion) is being developed by BioVersys for the treatment of serious infections due to *Acinetobacter baumannii* . Rifabutin (RBT) exerts potent antibacterial activity against *A. baumannii* under iron-limiting conditions[1,2]. RBT highjacks the *A. baumannii* siderophore receptor FhuE for active uptake enabling potent activity.

The goal was to identify the most important PK/PD index that correlates with efficacy and the estimates of index for the static, one- and two-log reductions in CFU.

METHODS

- MICs of rifabutin were measured on MHA + 0.1 mM PIH
- A single dose of BV100 (Rifabutin for infusion) was administered intravenously to neutropenic mice with a volume of 5 mL/kg.
- To describe the pharmacokinetics of BV100 in mice all samples were analyzed simultaneously using NONMEM 7.4.2 software.
- Model selection was based on a change in the objective function value (OFV), goodness-of-fit plots, parameter precision, shrinkage, visual predictive checks (VPC) and normalized prediction distribution errors (NPDE's).
- The population estimates of the final model were used in KINFUN to calculate the PK/PD indices, such as *f*AUC$_{0\text{-}24h}$/MIC, *f*C$_{max}$/MIC and *f*%T>MIC. Models were fitted without constraint if possible, and the fits were judged by R^2 values and visual inspection.
- A diagram of the procedures and summary of experiments in the reports is described below. Treatment was started 2h after infection (t=0) and continued for 24h (t=24h).



RESULTS

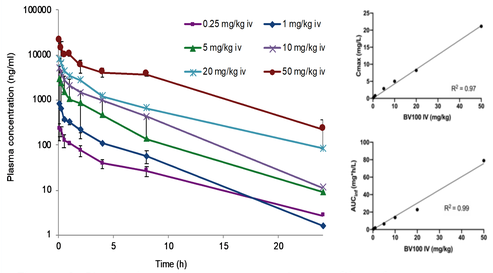


Figure 1. Single dose time-concentration profiles of mean plasma concentrations and dose proportionality plots of AUC$_{0\text{-}inf}$ and C$_{max}$ of rifabutin after iv administration

Parameter	Final model (RSE%) [shrinkage]	90% percentile bootstrap
Vc (L/kg)	1.83 (2)	1.61-2.07
CL (L/h/kg)	0.745 (2)	0.681-0.822
Vp (L/kg)	1.36 (3)	1.23-1.54
Q (L/h/kg)	1.31 (13)	1.04-1.73
Additional error (ng/mL)	2.39 (29)	0.10-3.60
Proportional error	0.159 (1)	0.128-0.183
IIV CL (%)	39.8 (12) [3]	30.0-44.9
IIV Vc (%)	58.0 (12) [6]	43.2-64.4

Table 1. Parameter estimates of the population pharmacokinetic and bootstrap (n=1000), central (Vc) and peripheral volume of distribution (Vp), clearance (CL), intercompartmental clearance (Q), interindividual clearance (IIV).

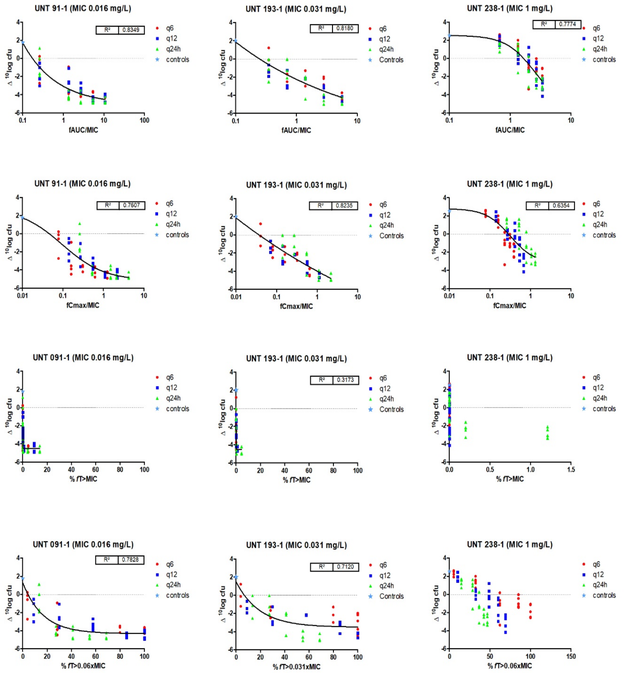


Figure 2. Relationships of BV100 24h *f*AUC/MIC, *f*C$_{max}$/MIC as well as %fT>MIC. Each dot represents a therapy response in one mouse thigh. The line is the best-fit line based on the sigmoidal E$_{max}$ model

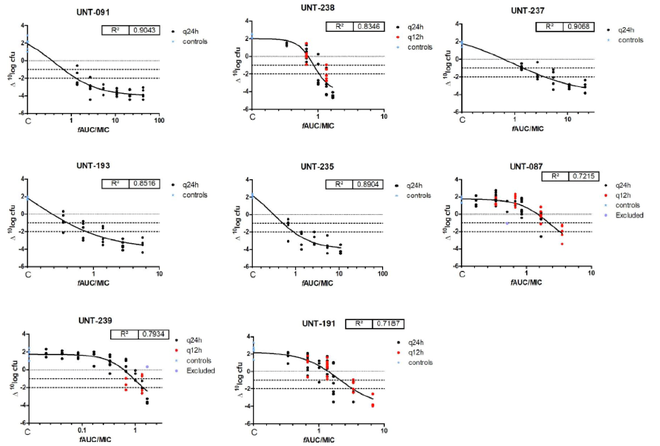


Figure 3. *f*AUC/MIC response relationships for eight *A. baumannii* strains.

Isolate	MIC	stasis	1-log kill	2-log kill
UNT235-1	0.008	0.61	0.75	0.95
UNT237-1	0.004	0.82	1.18	1.76
UNT087-1	4	1.19	1.41	1.66
UNT239-1	1	0.8	0.97	1.16
UNT191-1	2	1.16	1.39	1.69
UNT091-1	0.016	0.65	0.84	1.12
UNT193-1	0.031	0.54	0.68	0.90
UNT238-1	1	0.86	0.94	1.02
Mean (n=8)	-	0.83	1.02	1.28
Median (n=8)	-	0.81	0.95	1.14

Table 2. Estimates for *f*AUC/MIC for the isolates of the dose response analysis.

CONCLUSIONS

1. A population PK model was developed and the VPC, NPDE and bootstrap showed that the model adequately described the data.
2. The pharmacodynamic index of BV100 (rifabutin for infusion) that best correlated to efficacy in the *A. baumannii* neutropenic mouse lung infection model was the *f*AUC/MIC ratio.
3. The mean *f*AUC/MIC for a static effect was 0.83 and for a 1-log and 2-log reduction were 1.02 and 1.28, respectively.
4. The safety and tolerability of BV100 is currently being evaluated in Phase 1 clinical studies.

REFERENCES

1. Luna, B. *et al.* A nutrient-limited screen unmasks rifabutin hyperactivity for extensively drug-resistant *Acinetobacter baumannii*. *Nat. Microbiol.* 1–10 (2020).
2. Trebosc, V. *et al.* In vitro activity of rifabutin against 293 contemporary carbapenem-resistant *Acinetobacter baumannii* clinical isolates and characterization of rifabutin mode of action and resistance mechanisms. *J. Antimicrob. Chemother.* 75, 3552–3562 (2020).