In vivo efficacy of BV100 in mouse models of *Acinetobacter baumannii* infections

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INTRODUCTION

BV100 (rifabutin for infusion) is being developed by BioVersys for the treatment of serious infections due to *A. baumannii*. Screening of the ReFrame drug repurposing library under nutrient limiting conditions identified rifabutin as having potent antibacterial activity towards XDR *A. baumannii*[1]. Rifabutin (RBT), but not other rifamycins, uses the siderophore receptor FhuE to specifically enter *A. baumannii* in nutrient limiting conditions to finally exert its bactericidal activity by blocking the RNA synthesis (Figure 1)[2].

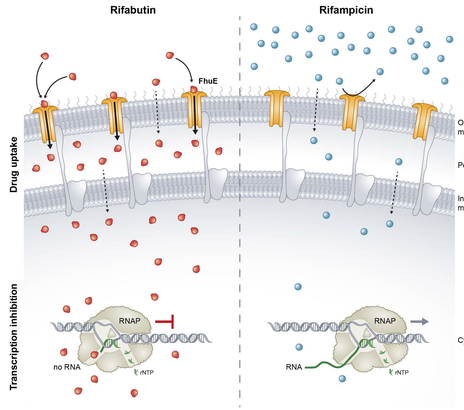

FIgure 1. Mode of action of RBT and rifampicin against *A. baumannii*.

This study aimed to determine the efficacy of BV100 in mouse lung infection models with eight diverse *A. baumannii* strains.

RESULTS

In vitro activity testing of rifabutin with *A. baumannii*

MICs of rifabutin were measured on MH-agar supplemented with 0.1 mM pyridoxal isonicotinoyl hydrazone (PIH) (Table 1). Strains with an MIC ranging from 0.004 – 4 mg/L were selected for efficacy testing in a neutropenic lung infection model.

Efficacy testing of BV100 (rifabutin for infusion) in a murine neutropenic lung infection model.

Neutropenic female CD-1 mice were inoculated intranasally with 6-7 $\log_{10}$ CFU of eight clinical *A. baumannii* strains to induce a lung infection. All models had a high bacterial burden at start of treatment (6.06 – 7.32 $\log_{10}$ CFU/lung), which further increased to >8 - 9 $\log_{10}$ CFU/lung within 24 hours in the non-treatment controls. A single IV dose of BV100 dose-dependently reduced the bacterial burden in the lungs for all strains tested. The mean maximum effect from start of treatment was -4.46 $\log_{10}$ CFU/lung for strain UNT238-1 and > 2.3 $\log_{10}$ reduction was observed for all isolates. IV administration of rifampicin at 10 or 20 mg/kg as control was less effective than a lower dose of BV100.

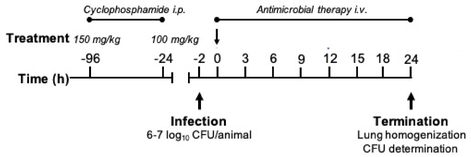

FIgure 2. Summary of the experimental procedure for the neutropenic lung infection model.

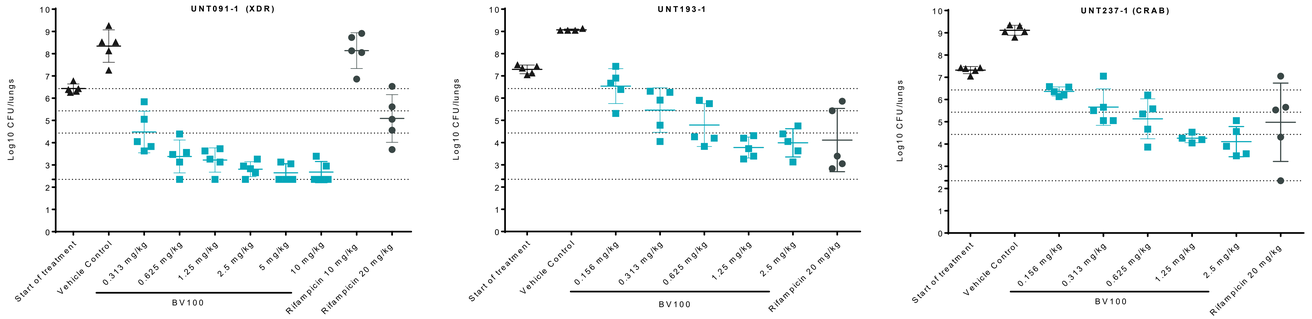

Figure 3. Neutropenic lung infection models with 3 diverse *A. baumannii* clinical isolates.

Table 1. Overview of clinical strains, their rifabutin MIC's and the efficacy readouts in the neutropenic lung infection models.

Clinical *A. baumannii* isolate	MIC (mg/L)	Mean $\log_{10}$ CFU/lung at start of treatment	Mean $\log_{10}$ CFU/lung at 24h untreated controls	BV100 maximum $\log_{10}$ CFU/lung reduction vs. start of treatment	Dose range tested (mg/kg)
UNT091-1	0.016	6.43	8.34	-3.79	0.313 - 10
UNT193-1	0.031	7.29	9.07	-3.51	0.156 - 2.5
UNT235-1	0.008	7.27	9.41	-4.14	0.156 - 2.5
UNT237-1	0.004	7.32	9.11	-3.21	0.156 - 2.5
UNT238-1	1	6.99	9.25	–4.46	10 - 50
UNT239-1	1	7.08	8.85	–2.39	10 - 50
UNT191-1	2	6.06	8.03	–3.72	20 - 200
UNT087-1	4	6.77	9.00	–2.08	20 - 200

Advantage of BV100 over oral rifabutin

- The oral bioavailability of rifabutin in patients is low and shows high variability[3].
- Oral rifabutin is strongly metabolized by intestinal CYP P450 enzymes.
- Therefore only low rifabutin drug exposures are achieved after oral administration
- **BV100 (rifabutin for infusion) has the potential to achieve high drug exposures with strongly reduced inter-subject variability.**

METHOD

Female CD-1 mice, 5-6 weeks old (body weight 18 – 22 g) were rendered neutropenic by intraperitoneal injection of 150 and 100 mg/kg cyclophosphamide on Day -4 and -1, respectively. Mice were anesthetized by IP injection of 0.2 mL of a Ketamine HCl (100mg/kg b.w.) + Xylazine (10 mg/kg b.w.) mixture, and intranasally infected by placing 0.05 mL drops of a bacterial *A. baumannii* culture onto the external nares. After inhalation of the bacteria, mice were placed into their cage to develop a bacterial lung infection. Dosing was started 2 h after infection and bacterial lung CFUs were determined 2 h (control) and 24 h post-infection. For CFU quantification animals were euthanized by CO_2 inhalation, the lungs were aseptically removed, placed in 2mL ice cold sterile PBS, homogenized, serially diluted and plated on appropriate culture media (BHI + 0.5% charcoal).

CONCLUSIONS

In MH-agar supplemented with 0.1 mM PIH, rifabutin shows an excellent *in vitro* activity against *A. baumannii*. This activity translates into a potent *in vivo* efficacy of BV100 towards diverse clinical *A. baumannii* isolates, including carbapenem and extensively drug resistant strains, in neutropenic lung infection models.

BioVersys develops BV100, a novel intravenous formulation of rifabutin, for the treatment of ventilator associated pneumonia caused by A. baumannii. The Safety and tolerability of BV100 is currently evaluated in Phase 1 clinical studies.

REFERENCES

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